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(54) Title: TRITERPENES HAVING FUNGICIDAL ACTIVITY AGAINST YEAST

(57) Abstract: Methods of treating a fungal or yeast infection and of killing or inhibiting fungi or yeast are disclosed. The methods use derivatives of triterpenes that are abundant in birch bark and other plants. The triterpenes include betulin, allobetulin, and lupeol.

TRITERPENES HAVING FUNGICIDAL ACTIVITY AGAINST YEAST

Background of the Invention

Betulin is a pentacyclic triterpenoid derived from the outer bark of paper birch trees (*Betula paperifera*). It can be present at concentrations of up to about 24% of the bark of white birch. *Merck Index*, twelfth edition, page 1236, 1996. Lupeol is a related compound also found in birch bark and in other plant sources. Lupeol is present at concentrations of about 1.5-3% of birch bark and at up to about 8.2% in *Canavalia ensiformis*, a plant widespread in the humid tropics of Asia, India, and Africa. Allobetulin is another triterpenoid found in birch bark. A typical pulp mill that processes birch produces enough bark waste to allow for the inexpensive isolation of significant quantities of these triterpenoids.

Fungi infect humans and are a major cause of human health problems. They also infect plants and cause enormous losses in agricultural productivity. One class of fungal infections of mammals are the dermatophytic infections. These are fungal infections of the hair, nails, and skin. They are caused by fungi called "dermatophytes," which include species belonging to the genera *Epidermophyton, Microsporum,* and *Trichophyton*. Among the species of dermatophytes are the following: *Microsporum canis*, which results in scalp and skin infections, mostly in children; *Microsporum gypseum*, which also results in scalp and skin infections in animals and humans; *Trichophyton tonsurans*, the major agent causing scalp ringworm; *Trichophyton rubrum*, causing skin, nail, hair, and scalp infections; and *Trichophyton mentagrophytes*, which can occur on all parts of the body surface.

Other fungal infectious agents include the opportunists that are likely to infect immunodeficient persons. These include *Cryptococcus, Candida*, and *Aspergillus*.

Betulin and related compounds have been shown to have anti-viral activity against herpes simplex virus. Carlson et al., U.S. Patent No. 5,750,578.

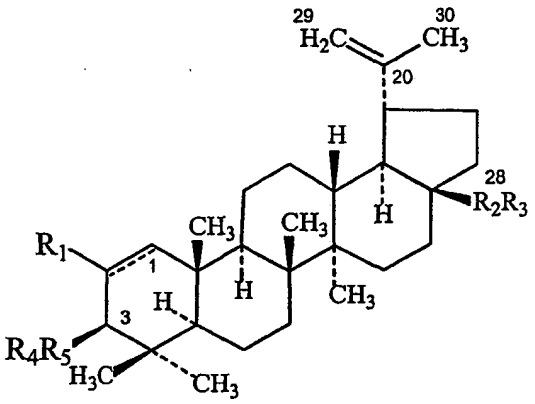
Current agents used to treat fungal infections include the polyene antibiotics, including nystatin; synthetic azoles; and griseofulvin. Fungal infections are difficult to treat because, like humans, they are eukaryotes.

Currently, there is a need for new anti-fungal and anti-yeast agents. A need particularly exists for agents that will act against a range of species, including dermatophytic fungi, yeasts,

and *Candida*. New anti-fungal agents would be less expensive to manufacture if they were abundant natural products or easily synthesized from abundant natural products.

Summary of the Invention

The present invention provides the use of a compound formula (I):



(I)

wherein

R_1 is hydrogen or hydroxy;

R_2 is a direct bond, carbonyl, oxy, thio, carbonyl oxy, oxy carbonyl, $(C_6$-$C_{10})$aryl, or $(C_1$-$C_6)$alkyl;

R_3 is hydrogen, hydroxy, $(C_1$-$C_6)$alkyl, $O=P(OH)_2$, $O=P(OH)_2OP(O)(OH)$-, $(C_1$-$C_5)$alkanoyl, $Si(R)_3$ wherein each R is H, phenyl or $(C_1$-$C_6)$alkyl, $C(O)N(R)_2$, benzyl, benzoyl, tetrahydropyran-2-yl, 1-[$(C_1$-$C_4)$alkoxy]$(C_1$-$C_4)$alkyl, or a glycoside;

R_4 is hydrogen, hydroxy, $(C_1$-$C_6)$alkyl, $O=P(OH)_2$, $O=P(OH)_2OP(O)(OH)$-, $(C_1$-$C_5)$alkanoyl, $Si(R)_3$ wherein each R is H, phenyl or $(C_1$-$C_6)$alkyl, $C(O)N(R)_2$, benzyl, benzoyl, tetrahydropyran-2-yl, 1-[$(C_1$-$C_4)$alkoxy]$(C_1$-$C_4)$alkyl, or a glycoside; or R_4 and R_5 together are oxo; and

R_5 is direct bond, carbonyl, oxy, thio, carbonyl oxy, oxy carbonyl, $(C_6$-$C_{10})$aryl, or $(C_1$-$C_6)$alkyl; or R_4 and R_5 together are oxo;

wherein any alkyl can optionally be substituted with one or more halo, hydroxy, $(C_6$-$C_{10})$aryl, nitro, cyano, $(C_1$-$C_6)$alkoxy, trifluoromethyl, polyethyleneimine, poly(ethylene glycol), oxo, NR_7R_8, wherein R_7 and R_8 are each independently hydrogen, $(C_1$-$C_6)$alkyl or

polyethyleneimine; or C(=O)OR$_9$, wherein R$_9$ is hydrogen, (C$_1$-C$_6$)alkyl, or polyethyleneimine;

each of the bonds represented by --- is independently absent or is present;

wherein any alkyl is optionally interrupted on carbon with one or more oxy, thio, sulfinyl, sulfonyl, polyethyleneimine, or poly(ethylene glycol);

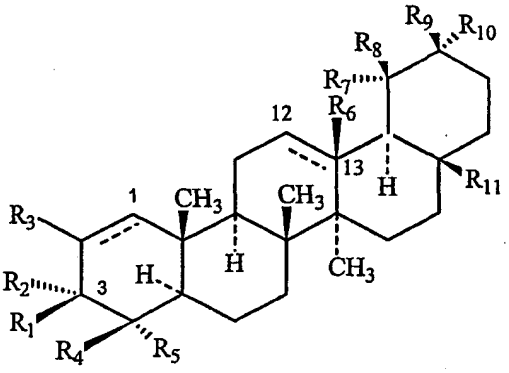
wherein any alkyl is optionally partially unsaturated;

wherein any aryl can optionally be substituted with one or more halo, hydroxy, nitro, cyano, (C$_1$-C$_6$)alkoxy, trifluoromethyl, polyethyleneimine, poly(ethylene glycol), oxo, NR$_7$R$_8$, wherein R$_7$ and R$_8$ are each independently hydrogen, (C$_1$-C$_6$)alkyl or polyethyleneimine; or C(=O)OR$_9$, wherein R$_9$ is hydrogen, (C$_1$-C$_6$)alkyl, or polyethyleneimine;

or a pharmaceutically acceptable salt thereof;

for the manufacture of a medicament for treating a mammal afflicted with a fungal or yeast infection.

The present invention also provides the use of a compound of formula (II):



(II)

wherein

one of R$_1$ and R$_2$ is -O-Y and the other is hydrogen or (C$_1$-C$_6$)alkyl optionally substituted by hydroxy, (C$_1$-C$_6$)alkoxy, halo, halo(C$_1$-C$_6$)alkoxy or NR$_j$R$_k$ wherein R$_j$ and R$_k$ are independently H, (C$_1$-C$_6$)alkyl or (C$_1$-C$_6$)alkonyl; or R$_1$ and R$_2$ together are oxo (=O);

R$_3$ is hydrogen, halo, carboxy, mercapto, (C$_1$-C$_6$)alkyl, (C$_3$-C$_8$)cycloalkyl, or -O-Y;

R$_4$ and R$_5$ are each independently hydrogen, (C$_1$-C$_6$)alkyl, or hydroxy(C$_1$-C$_6$)alkyl;

R$_6$ is hydrogen or is absent when the adjacent --- is a bond;

R_7 is hydrogen or $(C_1$-$C_6)$alkyl;

R_8 is hydrogen, $(C_1$-$C_6)$alkyl, or hydroxy$(C_1$-$C_6)$alkyl and R_{11} is hydrogen, $(C_1$-$C_6)$alkyl, carboxy, or hydroxy$(C_1$-$C_6)$alkyl; or R_8 and R_{11} together are -O-C(=X)-;

R_9 and R_{10}, are each independently hydrogen or $(C_1$-$C_6)$alkyl;

each of the bonds represented by --- is independently absent or is present;

X is two hydrogens, oxo (=O) or thioxo (=S);

each Y is independently H, aryl, $P(O)(Cl)_2$, $(C_3$-$C_8)$cycloalkyl, adamantyl, $-SO_2R_a$ $O=P(R_b)_2$, $O=P(R_c)_2OP(O)(R_d)$-, $Si(R_e)_3$, tetrahydropyran-2-yl, an amino acid, a peptide, a glycoside, or a 1 to 10 membered branched or unbranched carbon chain optionally comprising 1, 2, or 3 heteroatoms selected from non-peroxide oxy, thio, and $-N(R_f)$-; wherein said chain may optionally be substituted on carbon with 1, 2, 3, or 4 oxo (=O), hydroxy, carboxy, halo, mercapto, nitro, $-N(R_g)(R_h)$, $(C_3$-$C_8)$cycloalkyl, $(C_3$-$C_8)$cycloalkyloxy, aryl, aryloxy, adamantyl, adamantyloxy, hydroxyamino, trifluoroacetylamino, a glycoside, an amino acid, or a peptide; and wherein said chain may optionally be saturated or unsaturated (e.g. containing one, two, three or more, double or triple bonds);

R_a is $(C_1$-$C_6)$alkyl or aryl;

R_b, R_c, and R_d are each independently hydroxy, $(C_1$-$C_6)$alkoxy, hydroxy$(C_2$-$C_6)$alkoxy, adamantyloxy, adamantyl$(C_1$-$C_6)$alkoxy, norbornyloxy, 1,1-di(hydroxymethyl)-2-hydroxyethoxy, carboxy$(C_1$-$C_6)$alkoxy, 2,3-epoxypropyloxy, benzyloxy, $(C_3$-$C_8)$cycloalkyloxy, NR_xR_y, or aryloxy;

R_e is H, aryl or $(C_1$-$C_6)$alkyl;

R_f is hydrogen, $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$alkanoyl, phenyl or benzyl;

R_g and R_h are each independently selected from the group consisting of hydrogen, $(C_1$-$C_6)$alkyl, hydroxy$(C_1$-$C_6)$alkyl, adamantyl, adamantyl$(C_1$-$C_6)$alkyl, amino$(C_1$-$C_6)$alkyl, aminosulfonyl, $(C_1$-$C_6)$alkanoyl, aryl and benzyl; or R_b and R_c together with the nitrogen to which they are attached form a pyrrolidino, piperidino, or morpholino radical; and

R_x and R_y are each independently hydrogen, $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$alkanoyl, aryl or benzyl;

wherein each aryl of Y, R_a-R_d, R_g-R_h, R_x, and R_y may optionally be substituted by 1, 2, or 3 aminosulfonyl, carboxy, NR_iR_j, $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$alkoxy, hydroxy, halo, nitro,

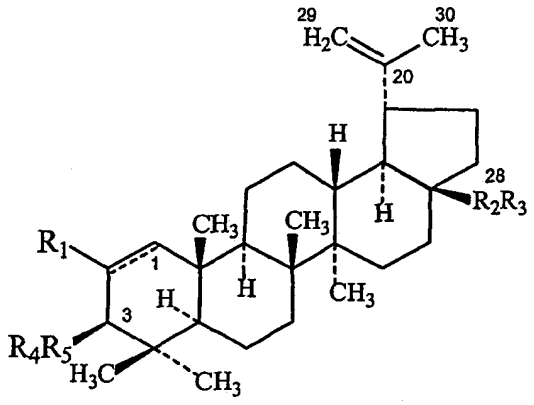
cyano, mercapto, carboxy, hydroxy(C_1-C_6)alkyl, halo(C_1-C_6)alkyl, trifluoromethoxy, (C_1-C_6)alkanoyl, (C_1-C_6)alkoxycarbonyl, (C_1-C_6)alkylthio, or (C_1-C_6)alkanoyloxy; wherein R_i and R_j are each independently hydrogen, (C_1-C_6)alkyl, (C_1-C_6)alkanoyl, phenyl, or benzyl;

wherein any alkyl can optionally be substituted with one or more polyethyleneimine or poly(ethylene glycol); and wherein any alkyl can optionally be interrupted with one or more polyethyleneimine or poly(ethylene glycol);

or a pharmaceutically acceptable salt thereof;

for the manufacture of a medicament for treating a mammal afflicted with a fungal or yeast infection.

The present invention also provides a method of inhibiting or killing a fungus or yeast, comprising contacting the fungus or yeast with an effective anti-fungal or anti-yeast amount of a triterpene of formula (I):



(I)

wherein

R_1 is hydrogen or hydroxy;

R_2 is a direct bond, carbonyl, oxy, thio, carbonyl oxy, oxy carbonyl, (C_6-C_{10})aryl, or (C_1-C_6)alkyl;

R_3 is hydrogen, hydroxy, (C_1-C_6)alkyl, $O=P(OH)_2$, $O=P(OH)_2OP(O)(OH)$-, (C_1-C_5)alkanoyl, $Si(R)_3$ wherein each R is H, phenyl or (C_1-C_6)alkyl, $C(O)N(R)_2$, benzyl, benzoyl, tetrahydropyran-2-yl, 1-[(C_1-C_4)alkoxy](C_1-C_4)alkyl, or a glycoside;

R_4 is hydrogen, hydroxy, $(C_1$-$C_6)$alkyl, $O=P(OH)_2$, $O=P(OH)_2OP(O)(OH)$-, $(C_1$-$C_5)$alkanoyl, $Si(R)_3$ wherein each R is H, phenyl or $(C_1$-$C_6)$alkyl, $C(O)N(R)_2$, benzyl, benzoyl, tetrahydropyran-2-yl, 1-[$(C_1$-$C_4)$alkoxy]$(C_1$-$C_4)$alkyl, or a glycoside; or R_4 and R_5 together are oxo; and

R_5 is direct bond, carbonyl, oxy, thio, carbonyl oxy, oxy carbonyl, $(C_6$-$C_{10})$aryl, or $(C_1$-$C_6)$alkyl; or R_4 and R_5 together are oxo;

wherein any alkyl can optionally be substituted with one or more halo, hydroxy, $(C_6$-$C_{10})$aryl, nitro, cyano, $(C_1$-$C_6)$alkoxy, trifluoromethyl, polyethyleneimine, poly(ethylene glycol), oxo, NR_7R_8, wherein R_7 and R_8 are each independently hydrogen, $(C_1$-$C_6)$alkyl or polyethyleneimine; or $C(=O)OR_9$, wherein R_9 is hydrogen, $(C_1$-$C_6)$alkyl, or polyethyleneimine;

each of the bonds represented by --- is independently absent or is present;

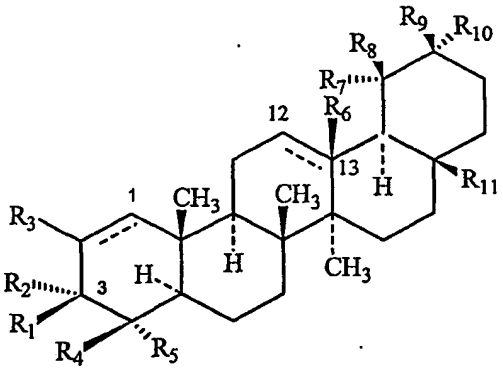
wherein any alkyl is optionally interrupted on carbon with one or more oxy, thio, sulfinyl, sulfonyl, polyethyleneimine, or poly(ethylene glycol);

wherein any alkyl is optionally partially unsaturated;

wherein any aryl can optionally be substituted with one or more halo, hydroxy, nitro, cyano, $(C_1$-$C_6)$alkoxy, trifluoromethyl, polyethyleneimine, poly(ethylene glycol), oxo, NR_7R_8, wherein R_7 and R_8 are each independently hydrogen, $(C_1$-$C_6)$alkyl or polyethyleneimine; or $C(=O)OR_9$, wherein R_9 is hydrogen, $(C_1$-$C_6)$alkyl, or polyethyleneimine;

or a pharmaceutically acceptable salt thereof.

The present invention also provides a method of inhibiting or killing a fungus or yeast comprising contacting the fungus or yeast with an effective anti-fungal or anti-yeast amount of a triterpene of formula (II):



(II)

wherein

one of R_1 and R_2 is -O-Y and the other is hydrogen or $(C_1$-$C_6)$alkyl optionally substituted by hydroxy, $(C_1$-$C_6)$alkoxy, halo, halo$(C_1$-$C_6)$alkoxy or NR_jR_k wherein R_j and R_k are independently H, $(C_1$-$C_6)$alkyl or $(C_1$-$C_6)$alkonyl; or R_1 and R_2 together are oxo (=O);

R_3 is hydrogen, halo, carboxy, mercapto, $(C_1$-$C_6)$alkyl, $(C_3$-$C_8)$cycloalkyl, or -O-Y;

R_4 and R_5 are each independently hydrogen, $(C_1$-$C_6)$alkyl, or hydroxy$(C_1$-$C_6)$alkyl;

R_6 is hydrogen or is absent when the adjacent --- is a bond;

R_7 is hydrogen or $(C_1$-$C_6)$alkyl;

R_8 is hydrogen, $(C_1$-$C_6)$alkyl, or hydroxy$(C_1$-$C_6)$alkyl and R_{11} is hydrogen, $(C_1$-$C_6)$alkyl, carboxy, or hydroxy$(C_1$-$C_6)$alkyl; or R_8 and R_{11} together are -O-C(=X)-;

R_9 and R_{10}, are each independently hydrogen or $(C_1$-$C_6)$alkyl;

each of the bonds represented by --- is independently absent or is present;

X is two hydrogens, oxo (=O) or thioxo (=S);

each Y is independently H, aryl, $P(O)(Cl)_2$, $(C_3$-$C_8)$cycloalkyl, adamantyl, $-SO_2R_a$ $O=P(R_b)_2$, $O=P(R_c)_2OP(O)(R_d)$-, $Si(R_e)_3$, tetrahydropyran-2-yl, an amino acid, a peptide, a glycoside, or a 1 to 10 membered branched or unbranched carbon chain optionally comprising 1, 2, or 3 heteroatoms selected from non-peroxide oxy, thio, and $-N(R_f)$-; wherein said chain may optionally be substituted on carbon with 1, 2, 3, or 4 oxo (=O), hydroxy, carboxy, halo, mercapto, nitro, $-N(R_g)(R_h)$, $(C_3$-$C_8)$cycloalkyl, $(C_3$-$C_8)$cycloalkyloxy, aryl, aryloxy, adamantyl, adamantyloxy, hydroxyamino, trifluoroacetylamino, a glycoside, an amino acid, or a peptide; and wherein said chain may optionally be saturated or unsaturated (e.g. containing one, two, three or more, double or triple bonds);

R_a is $(C_1$-$C_6)$alkyl or aryl;

R_b, R_c, and R_d are each independently hydroxy, $(C_1$-$C_6)$alkoxy, hydroxy$(C_2$-$C_6)$alkoxy, adamantyloxy, adamantyl$(C_1$-$C_6)$alkoxy, norbornyloxy, 1,1-di(hydroxymethyl)-2-hydroxyethoxy, carboxy$(C_1$-$C_6)$alkoxy, 2,3-epoxypropyloxy, benzyloxy, $(C_3$-$C_8)$cycloalkyloxy, NR_xR_y, or aryloxy;

R_e is H, aryl or $(C_1$-$C_6)$alkyl;

R_f is hydrogen, $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$alkanoyl, phenyl or benzyl;

R_g and R_h are each independently selected from the group consisting of hydrogen, $(C_1$-$C_6)$alkyl, hydroxy$(C_1$-$C_6)$alkyl, adamantyl, adamantyl$(C_1$-$C_6)$alkyl, amino$(C_1$-$C_6)$alkyl, aminosulfonyl, $(C_1$-$C_6)$alkanoyl, aryl and benzyl; or R_b and R_c together with the nitrogen to which they are attached form a pyrrolidino, piperidino, or morpholino radical; and

R_x and R_y are each independently hydrogen, $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$alkanoyl, aryl or benzyl;

wherein each aryl of Y, R_a-R_d, R_g-R_h, R_x, and R_y may optionally be substituted by 1, 2, or 3 aminosulfonyl, carboxy, NR_iR_j, $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$alkoxy, hydroxy, halo, nitro, cyano, mercapto, carboxy, hydroxy$(C_1$-$C_6)$alkyl, halo$(C_1$-$C_6)$alkyl, trifluoromethoxy, $(C_1$-$C_6)$alkanoyl, $(C_1$-$C_6)$alkoxycarbonyl, $(C_1$-$C_6)$alkylthio, or $(C_1$-$C_6)$alkanoyloxy; wherein R_i and R_j are each independently hydrogen, $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$alkanoyl, phenyl, or benzyl;

wherein any alkyl can optionally be substituted with one or more polyethyleneimine or poly(ethylene glycol); and wherein any alkyl can optionally be interrupted with one or more polyethyleneimine or poly(ethylene glycol);

or a pharmaceutically acceptable salt thereof.

The invention provides novel compounds of formula (I) and formula (II), as well as intermediates for the synthesis of compounds of formula (I) and formula (II). The invention also provides compounds of formula (I) and (II) that are useful as intermediates for the synthesis of other useful compounds. The invention provides the use of compounds of formula (I) and formula (II) for the manufacture of medicaments useful for the treatment of bacterial infections in a mammal, such as a human. The invention also provides processes for preparing compounds of formula (I) and formula (II).

Brief Description of the Figures

FIG. 1 is a graphical depiction of the results of growth inhibition studies on *Trichophyton mentagrophytes* in liquid culture with various derivatives of lupeol.

Detailed Description

The following definitions are used, unless otherwise described: halo is fluoro, chloro, bromo, or iodo. Alkyl, alkoxy, alkenyl, etc. denote both straight and branched groups; but

reference to an individual radical such as "propyl" embraces only the straight chain radical, a branched chain isomer such as "isopropyl" being specifically referred to. Aryl denotes a phenyl radical or an ortho-fused bicyclic carbocyclic radical having about nine to ten ring atoms in which at least one ring is aromatic.

It will be appreciated by those skilled in the art that compounds of the invention having a chiral center may exist in and be isolated in optically active and racemic forms. Some compounds may exhibit polymorphism. It is to be understood that the present invention encompasses any racemic, optically-active, polymorphic, or stereoisomeric form, or mixtures thereof, of a compound of the invention, which possess the useful properties described herein, it being well known in the art how to prepare optically active forms (for example, by resolution of the racemic form by recrystallization techniques, by synthesis from optically-active starting materials, by chiral synthesis, or by chromatographic separation using a chiral stationary phase) and how to determine antibacterial activity using the standard tests described herein, or using other similar tests which are well known in the art.

Specific and preferred values listed below for radicals, substituents, and ranges, are for illustration only; they do not exclude other defined values or other values within defined ranges for the radicals and substituents

Specifically, $(C_1\text{-}C_6)$alkyl can be methyl, ethyl, propyl, isopropyl, butyl, iso-butyl, sec-butyl, pentyl, 3-pentyl, or hexyl; partially unsaturated $(C_2\text{-}C_6)$alkyl or $(C_2\text{-}C_6)$alkenyl can be vinyl, 1-propenyl, 2-propenyl, 1-butenyl, 2-butenyl, 3-butenyl, 1,-pentenyl, 2-pentenyl, 3-pentenyl, 4-pentenyl, 1- hexenyl, 2-hexenyl, 3-hexenyl, 4-hexenyl, or 5-hexenyl; $(C_1\text{-}C_5)$alkanoyl can be carbonyl, acetyl, propanoyl, butanoyl, isopropanoyl, or pentenoyl; $(C_1\text{-}C_6)$alkoxy can be methoxy, ethoxy, propoxy, isopropoxy, butoxy, iso-butoxy, sec-butoxy, pentoxy, 2-pentoxy, 3-pentoxy, or hexyloxy; halo$(C_1\text{-}C_6)$alkoxy can be trifluoromethyloxy, 2-chloroethyloxy, 3,3-dichloropropyloxy, or 4,4,4-trifluorobutyloxy; $(C_3\text{-}C_8)$cycloalkyl can be cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, or cyclooctyl; $(C_3\text{-}C_8)$cycloalkyloxy can be cyclopropyloxy, cyclobutyloxy, cyclopentyloxy, cyclohexyloxy, cycloheptyloxy, or cyclooctyloxy; hydroxy$(C_1\text{-}C_6)$alkoxy can be hydroxymethoxy, 1-hydroxyethoxy, 2-hydroxyethoxy, 1-hydroxypropoxy, 2-hydroxypropoxy, 3-hydroxypropoxy, 1-hydroxybutoxy, 4-hydroxybutoxy, 1-hydroxypentoxy, 5-hydroxypentoxy, 1-hydroxyhexoxy, or 6-hydroxyhexoxy;

amino(C_1-C_6)alkyl can be aminomethyl, 1-aminoethyl, 2-aminoethyl, 1-aminopropyl, 2-aminopropyl, 3-aminopropyl, 1-aminobutyl, 2-aminobutyl, 3-aminobutyl, 4-aminobutyl, 1-aminopentyl, 2-aminopentyl, 3-aminopentyl, 5-aminopentyl, 1-aminohexyl, 2-aminohexyl, 3-aminohexyl, or 6-aminohexyl; (C_1-C_6)alkoxycarbonyl can be methoxycarbonyl, ethoxycarbonyl, propyloxycarbonyl, isopropyloxycarbonyl, 2-methylpropyloxycarbonyl, butyloxycarbonyl, pentyloxycarbonyl, or hexyloxycarbonyl; (C_1-C_6)alkanoyloxy can be carbonyloxy, acetyloxy, propanoyloxy, butanoyloxy, 2-methylpropanoyloxy, 2-methylbutanoyloxy, 3-methylbutanoyloxy, pentanoyloxy, or hexanoyloxy.

"3-Carboxypropenoyloxymethyl" refers to the structure $-CH_2OC(=O)CH=CHCOOH$.

"Aminoacetoxymethyl" refers to the structure $-CH_2OC(=O)CH_2NH_2$.

"(Carboxymethoxy)acetoxymethyl" refers to the structure $-CH_2OC(=O)CH_2OCH_2COOH$.

"4-Carboxybutanoyloxymethyl" refers to the structure $-CH_2OC(=O)CH_2CH_2CH_2COOH$.

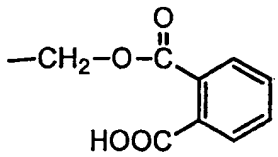
"3-Carboxypropanoyloxymethyl" refers to the structure $-CH_2OC(=O)CH_2CH_2COOH$.

"Carboxycarbonyloxymethyl" refers to the structure $-CH_2OC(=O)COOH$.

"2-Amino-3-methyl-butanoyloxymethyl" refers to the structure $-CH_2OC(=O)CH(NH_2)CH(CH_3)_2$.

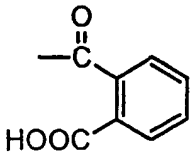
"4-Carboxy-(3,3-dimethyl)butanoyloxymethyl" refers to the structure - $CH_2OC(=O)CH_2C(CH_3)_2CH_2COOH$.

"2-Carboxybenzoyloxymethyl" refers to the structure



"Butanoyloxymethyl" refers to the structure $-CH_2OC(=O)CH_2CH_2CH_3$.

"2-Carboxybenzoyl" refers to the structure



"2-Amino-3-methylbutanoyl" refers to the structure $-C(=O)CH_2(NH_2)CH_2(CH_3)_2$.

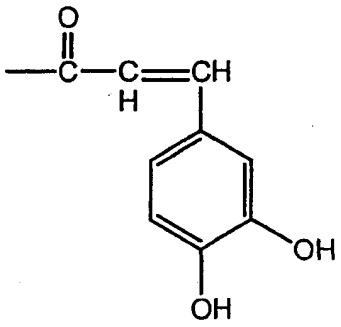
"3-Carboxypropenoyl" refers to the structure -C(=O)CH=CHCOOH.

"Aminoacetyl" refers to the structure $-C(=O)CH_2NH_2$.

"4-Carboxybutanoyl" refers to the structure $-C(=O)CH_2CH_2CH_2COOH$.

"(Carboxymethoxy)acetyl" refers to the structure $-C(=O)CH_2OCH_2COOH$.

"3-(3,4-Dihydroxyphenyl)propenoyl" refers to the structure



"3-Carboxypropanoyl" refers to the structure $-C(=O)CH_2CH_2COOH$.

"Carboxycarbonyl" refers to the structure -C(=O)COOH.

"4-Carboxy-(3,3-dimethyl)butanoyl" refers to the structure $-C(=O)CH_2C(CH_3)_2CH_2COOH$.

"Carboxymethylenethioacetyl" refers to the structure $-C(=O)CH_2SCH_2COOH$.

"3-Carboxy-3-methylbutanoyl" refers to the structure $-C(=O)CH_2C(COOH)(CH_3)_2$.

The term "amino acid," comprises the residues of the natural amino acids (e.g. Ala, Arg,

Asn, Asp, Cys, Glu, Gln, Gly, His, Hyl, Hyp, Ile, Leu, Lys, Met, Phe, Pro, Ser, Thr, Trp, Tyr, and Val) in D or L form, as well as unnatural amino acids (e.g. phosphoserine, phosphothreonine, phosphotyrosine, hydroxyproline, gamma-carboxyglutamate; hippuric acid, octahydroindole-2-carboxylic acid, statine, 1,2,3,4,-tetrahydroisoquinoline-3-carboxylic acid, penicillamine, ornithine, citruline, α-methyl-alanine, para-benzoylphenylalanine, phenylglycine, propargylglycine, sarcosine, and tert-butylglycine). The term also comprises natural and unnatural amino acids bearing a conventional amino protecting group (e.g. acetyl or benzyloxycarbonyl), as well as natural and unnatural amino acids protected at the carboxy terminus (e.g. as a $(C_1$-$C_6)$alkyl, phenyl or benzyl ester or amide; or as an α-methylbenzyl amide). Other suitable amino and carboxy protecting groups are known to those skilled in the art (See for example, T.W. Greene, *Protecting Groups In Organic Synthesis*; Third Edition, Wiley: New York, 1999, and references cited therein). An amino acid can be linked to the remainder of a compound of formula (I) or (II) through the carboxy terminus, the amino terminus, or through any other convenient point of attachment, such as, for example, through the sulfur of cysteine.

The term "peptide" describes a sequence of 2 to 25 amino acids (e.g. as defined hereinabove) or peptidyl residues. The sequence may be linear or cyclic. For example, a cyclic peptide can be prepared or may result from the formation of disulfide bridges between two cysteine residues in a sequence. A peptide can be linked to the remainder of a compound of formula I or II through the carboxy terminus, the amino terminus, or through any other convenient point of attachment, such as, for example, through the sulfur of a cysteine. Preferably a peptide comprises 3 to 25, or 5 to 21 amino acids. Peptide derivatives can be prepared as disclosed in U.S. Patent Numbers 4,612,302; 4,853,371; and 4,684,620.

Glycosides are formed by reacting mono-, di- and polysaccharides with 1-2 hydroxyl groups of the compound of formula (I) or formula (II), including glucose, glucuronic acid, mannose, galactose, sorbase, ribose, maltose, sucrose, modified cellulosics, dextrans, modified starches and the like. These derivatives can advantageously exhibit improved water solubility over betulin itself. See, *Remington's Pharmaceutical Sciences*, A. R. Gennaro, ed., Mack Pub. Co. (18th ed., 1990) at pages 384-386. Glycoside derivatives can be prepared as described in PCT Applications WO 96/34005 and 97/03995.

The term "polyethyleneimine" refers to the group $(-NHCH_2CH_2-)_x[-$

$N(CH_2CH_2NH_2)CH_2CH_2-]_y$. Polyethyleneimine can be attached to a compound through either of the nitrogen atoms marked with hash marks. "Poly(ethylene glycol)" refers to the compound $H(OCH_2CH_2)_nOH$. It can be attached to a compound through its terminal hydroxyl.

The term "partially unsaturated" refers to a linear or branched hydrocarbon having one or more carbon-carbon double bonds.

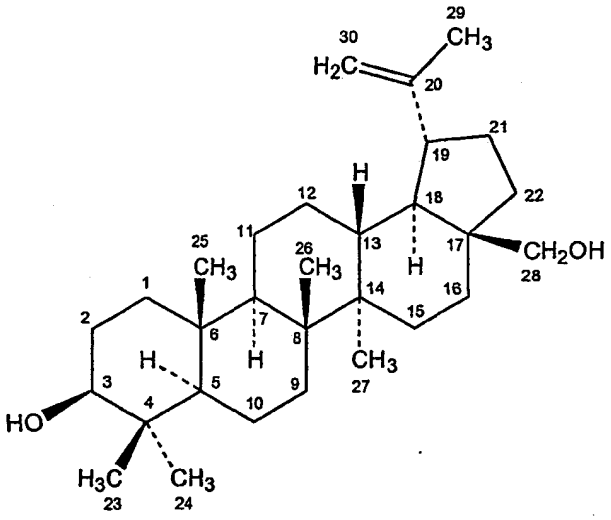
The term "phosphono" refers to $O=P(OH)_2-$.

The term "direct bond" refers to a group being absent.

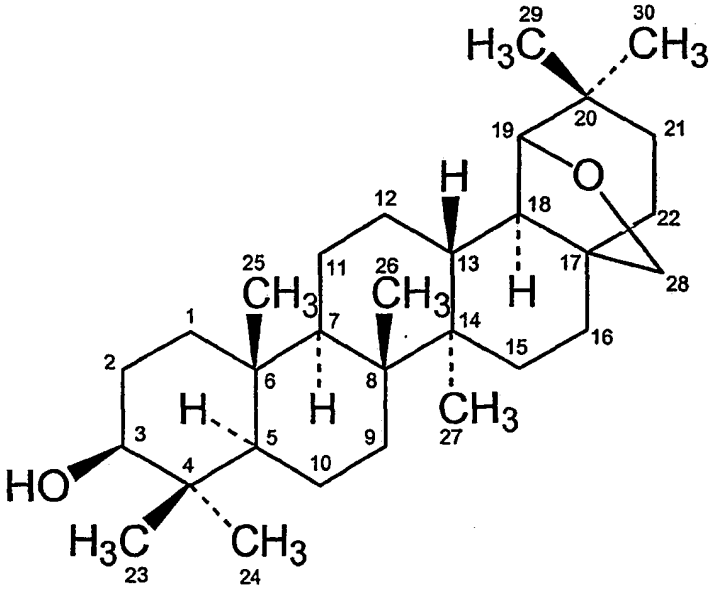
Combinations of substituents and/or variables are permissible only if such combinations result in stable compounds. By "stable compound" is meant herein a compound that is sufficiently robust to survive isolation to a useful degree of purity from a reaction mixture, and formulation into an efficacious antifungal agent.

The term "fungus" refers to a distinct group of eukaryotic, spore-forming organisms wih absorptive nutrition and lacking chlorophyll. It includes mushrooms, molds, and yeasts.

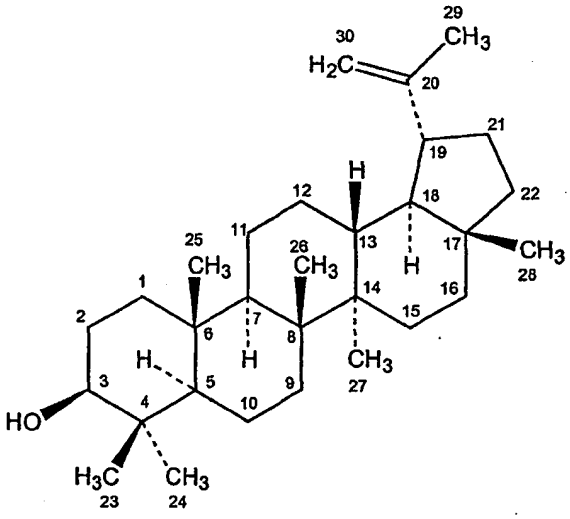
The structure and carbon numbering of three exemplary compounds of the present invention are shown below.



Betulin



Allobetulin



Lupeol

Specific values for compounds of formula (I) are as follows.

A specific value for the bond between carbons 1 and 2 is a single bond.

Another specific value for the bond between carbons 1 and 2 is a double bond.

A specific value for R_1 is hydrogen.

Another specific value for R_1 is hydroxy.

A specific value for R_2 is a direct bond.

A specific value for R_3 is $(C_1\text{-}C_6)$alkyl; wherein any alkyl can optionally be substituted with one or more oxo, carboxy, amino, $-OP(=O)(OH)_2$, or phenyl; any alkyl is optionally interrupted on carbon with one or more oxy or thio; any alkyl is optionally partially unsaturated; and any aryl can optionally be substituted with one or more hydroxy or carboxy.

Another specific value for R_3 is hydroxymethyl, (carboxymethoxy)acetoxymethyl, 4-carboxybutanoyloxymethyl, 3-carboxypropenoyloxymethyl, 2-carboxybenzoyloxymethyl, 3-carboxypropanoyloxymethyl, aminoacetoxymethyl, carboxycarbonyloxymethyl, 2-amino-3-methyl-butanoyloxymethyl, 4-carboxy-(3,3-dimethyl)butanoyloxymethyl, or $-CH_2OC(=O)C(=O)\text{-}(\text{-}NHCH_2CH_2)_x\text{-}[\text{-}N(CH_2CH_2NH_2)CH_2CH_2]_y$.

A specific value for R_4 is hydrogen or $(C_1\text{-}C_6)$alkyl; wherein any alkyl can optionally be substituted with one or more oxo, carboxy, amino, $-OP(=O)(OH)_2$, or phenyl; any alkyl is optionally interrupted on carbon with one or more oxy or thio; any alkyl is optionally partially unsaturated; and any aryl can optionally be substituted with one or more hydroxy or carboxy.

Another specific value for R_4 is hydrogen, hydroxymethyl, (carboxymethoxy)acetyl, 4-carboxybutanoyl, 3-carboxypropenoyl, 2-carboxybenzoyl, 3-carboxypropanoyl, aminoacetyl, carboxycarbonyl, 2-amino-3-methyl-butanoyl, 4-carboxy-(3,3-dimethyl)butanoyl, 3-carboxy-3-methylbutanoyl or $-C(=O)C(=O)\text{-}(\text{-}NHCH_2CH_2)_x\text{-}[\text{-}N(CH_2CH_2NH_2)CH_2CH_2]_y$.

A specific value for R_5 is oxy.

A specific group of compounds are compounds of formula (I) wherein R_1 is hydrogen or hydroxy; R_2 is a direct bond; R_3 is $(C_1\text{-}C_6)$alkyl; R_4 is hydrogen or $(C_1\text{-}C_6)$alkyl; and R_5 is oxy or R_4 and R_5 together are oxo; wherein any alkyl can optionally be substituted with one or more oxo, carboxy, amino, or $-OP(=O)(OH)_2$, or phenyl; any alkyl is optionally interrupted on carbon with one or more oxy or thio; any alkyl is optionally partially unsaturated; and any aryl can optionally be substituted with one or more hydroxy or carboxy.

Another specific group of compounds are compounds of formula (I) wherein R_1 is hydrogen or hydroxy; R_2 is a direct bond; R_3 is hydroxymethyl, (carboxymethoxy)acetoxymethyl, 4-carboxybutanoyloxymethyl, 3-carboxypropenoyloxymethyl, 2-carboxybenzoyloxymethyl, 3-carboxypropanoyloxymethyl, aminoacetoxymethyl, carboxycarbonyloxymethyl, 2-amino-3-methyl-butanoyloxymethyl, 4-carboxy-(3,3-dimethyl)butanoyloxymethyl, or $-CH_2OC(=O)C(=O)-(-NHCH_2CH_2)_x-[-N(CH_2CH_2NH_2)CH_2CH_2]_y$; R_4 is hydrogen, hydroxymethyl, (carboxymethoxy)acetyl, 4-carboxybutanoyl, 3-carboxypropenoyl, 2-carboxybenzoyl, 3-carboxypropanoyl, aminoacetyl, carboxycarbonyl, 2-amino-3-methyl-butanoyl, 4-carboxy-(3,3-dimethyl)butanoyl, 3-carboxy-3-methylbutanoyl or $-C(=O)C(=O)-(-NHCH_2CH_2)_x-[-N(CH_2CH_2NH_2)CH_2CH_2]_y$.; and R_5 is oxy or R_4 and R_5 together are oxo.

Another specific group of compounds of formula (I) is betulin; betulin-3,28-diglycine; betulin-28-glycerol oxalate; betulin-28-glycine; betulin-28-oxalate; betulin arabinose galactan; betulin-3,28-diglycolate; betulin-3-maleate; betulin-3,28-di-(L-glutamic acid γ-benzylester) ester; betulin-3,28-di-L-alanine; betulin-3,28-di-L-proline ester; betulin3,28-dioxalate; betulin-1-ene-2-ol; betulin-3,28-diphenylalanine; betulin-3,28-di-(L-proline ester); betulin-3,28- dioxalate-polyethylene amine; betulin-3,28-diphosphate; betulin-3-caffeate; betulin-3,28-(3',3'-dimethyl)glutarate; betulin-28-diglycolate; betulin-28-glutarate; betulin-28-maleate; betulin-28-phthalate; betulin-3,28-di(3',3'-dimethyl) glutarate; betulin-3,28-didiglycolate; betulin-3,28-dithiodiglycolate; betulin-3,28-diglutarate; betulin-3,28-dimaleate; betulin-3,28-diglycolate; betulin-3,28-diphthalate; betulin-3,28-di-L-valine ester; betulin-28-succinate; betulin-3,28-disuccinate; betulin-3,28-di-(polyethylene glycol)-COOH (Mw=1448); betulin-3,28-di-(polyethylene glycol)-COOH (Mw=906 crude); betulin-3,28-di-(polyethylene glycol)-COOH (Mw=906 pure); betulinic acid; betulon-1-ene-2-ol; betulin-3,28-(dipoly(ethylene glycol)bis (carboxymethylester); hederin hydrate; lupeol; lupeol-3-glutarate; lupeol-3-succinate; lupeol-3-thiodiglycolate; lupeol-3-phthalate; oleanolic acid; ursolic acid; or uvaol.

Another specific group of compounds of formula (I) is betulin; betulin-3,28-diglycine; betulin-28-glycerol oxalate; betulin-28-glycine; betulin oxalate; betulin arabinose galactan; betulin-3,28-diglycolate; betulin-3-maleate; betulin di-(L-glutamic acid γ-benzylester) ester; betulin 3,28-di-L-alanine; betulin3,28-di-L-proline; betulin-3,28-dioxalate; betulin-1-ene-2-ol;

betulin-3,28-diphenylalanine ester; betulin-3,28-dioxalate-(polyethylene amine); betulin-3-caffeate; betulin-3,28-(3',3'-dimethyl)glutarate; betulin-28-diglycolate; betulin-28-glutarate; betulin-28-phthalate; betulin-3,28-diglycolate; betulin-3,28-diphthalate; betulin-3,28-phosphate; betulin-28-succinate; betulin-3,28-disuccinate; betulin-3,28-di-(polyethylene glycol)-COOH (Mw=1448); betulin-3,28-di-(polyethylene glycol)-COOH (Mw=906 crude); betulin-3,28-di-(polyethylene glycol)-COOH (Mw=906 pure); betulon-1-ene-2-ol; betulin-3,28-(dipoly(ethylene glycol)bis(carboxymethylester); hederin hydrate; lupeol-3-succinate; lupeol-3-phthalate; lupeol-3-glutarate; oleanolic acid; ursolic acid; or uvaol.

Another specific group of compounds of formula (I) is betulin; betulin-3-maleate; betulin-28-diglycolate; betulin-28-glutarate; betulin-28-maleate; betulin-28-phthalate; betulin-28-succinate; betulin-3,28-diglycine; betulin-3,28-didiglycolate; betulin-3,28-dimaleate; betulin-3,28-dioxalate-3-polyethyleneimine; betulin-3,28-di(3',3'-dimethyl)glutarate; betulin-3,28-dioxalate-3,28-polyethyleneimine; betulin-3,28-diphthalate; betulin-3,28-disuccinate; betulin-3,28-di-L-valine; lupeol; lupeol-3-amine; lupeol-3-(3',3'-dimethyl)succinate; lupeol-3-maleate; lupenone; or lupenon-1,2-ene-2-ol.

Specific values for the compounds of formula (II) are as follows.

A specific value for the bond between carbons 1 and 2 is a single bond.

A specific value for R_1 is -O-Y, wherein Y is hydrogen, an amino acid, or $(C_1$-$C_6)$alkyl; wherein any alkyl can be optionally substituted with one or more oxo, hydroxy, amino, phenyl, or carboxy any alky can be optionally interrupted with one or more oxy or thio; any phenyl can be optionally substituted with one or more hydroxy or carboxy.

Another specific value for R_1 is -O-Y, wherein Y is hydrogen, 3-carboxypropanoyl, 4-carboxybutanoyl, or 2-amino-2-methylbutanoyl.

A specific value for R_2 is hydrogen.

A specific value for R_3 is hydrogen.

A specific value for R_4 is methyl.

A specific value for R_5 is methyl.

A specific value for R_6 is hydrogen.

A specific value for the bond between carbons 12 and 13 is a single bond.

A specific value for R_7 is hydrogen.

A specific value for R_8 and R_{11} together is -O-CH_2-.

A specific value for R_9 is methyl.

A specific value for R_{10} is methyl.

A specific group of compounds of formula (II) is the compounds wherein R_1 is -O-Y and Y is hydrogen, an amino acid, or (C_1-C_6)alkyl; wherein the alkyl of Y can be optionally substituted with one or more oxo, hydroxy, amino, carboxy, or phenyl optionally substituted with one or more hydroxy or carboxy; and can be optionally interrupted with one or more oxy or thio; R_2 is hydrogen; R_3 is hydrogen and the bond between carbons 1 and 2 is a single bond; R_4 and R_5 are each methyl; R_6 is hydrogen and the bond between carbons 12 and 13 is a single bond; R_7 is hydrogen; R_8 and R_{11} together are -O-CH_2-; and R_9 and R_{10} are each methyl.

Another specific group of compounds of formula (II) is 3-β-acetoxy-19αH-19,28 lactone oleanan; allobetulin; allobetulin-3-succinate; allobetulin-3-glycine; allobetulin lactone; allobetulin lactone-3-acetate; allobetulin lactone-3-phosphate; allobetulin-3-L-alanine; allobetulin-3-L-valine; allobetulin-3-L-proline ester; allobetulin-3-succinate; allobetulin-3-diglycolate; allobetulin-3-phthalate; allobetulin-3-methylenamine; allobetulin-3-ethanolamine; allobetulin-3-glycolate; allobetulin-3-glutarate; allobetulin-28-glutarate; allobetulin-3-methylamine HCl; allobetulin-3-phosphate; allobetulin-3-(polyethylene glycol)-COOH (Mw=674); allobetulon; allobetulon lactone-1-ene-2-ol; allobetulon lactone-1-en-2-succinate; allobetulon-1-ene-2-ol; allobetulon-1-ene-2-diglycolate; 3-allobetulon-1-ene-2-succinate; allobetulin-3-(poly(ethylene glycol)bis (carboxymethyl ester); or 3-allobetulon-1-ene-2-diglycolate.

Another specific group of compounds of formula (II) is 3-β-acetoxy-19αH-19,28 lactone oleanan; allobetulin; allobetulin-3-succinate; allobetulin lactone; allobetulin lactone-3-acetate; allobetulin lactone-3-phosphate; allobetulin-3-L-valine; allobetulin-3-L-proline; allobetulin-3-succinate; allobetulin-3-diglycolate; allobetulin-3-methylenamine; allobetulin-3-ethanolamine; allobetulin-3-glycolate; allobetulin-3- glutarate; allobetulin-3-glutarate; allobetulin-3-(polyethylene glycol)-COOH (Mw=674); allobetulon; allobetulon lactone-1-ene-2-ol; allobetulon lactone-1-en-2-succinate; allobetulon-1-ene-2-ol; allobetulon-1-ene-2-diglycolate; 3-allobetulon-1-ene-2-succinate; or allobetulin-3-(poly(ethylene glycol)bis(carboxymethyl ester).

Another specific group of compounds of formula (II) is allobetulin, allobetulin-3-

glutarate, allobetulin-3-succinate, or allobetulin-3-L-valine.

A specific method of the invention is the method of treating a mammal afflicted with a fungal or yeast infection comprising administering to the mammal an effective anti-fungal or anti-yeast amount of a compound of formula (I) or formula (II) wherein the mammal is a human.

Another specific method of the invention is the method of treating a mammal afflicted with a fungal or yeast infection comprising administering to the mammal an effective anti-fungal or anti-yeast amount of a compound of formula (I) or formula (II) wherein the fungal infection is caused by a dermatophytic fungus.

Another specific method of the invention is the method of treating a mammal afflicted with a fungal or yeast infection comprising administering to the mammal an effective anti-fungal or anti-yeast amount of a compound of formula (I) or formula (II) wherein the fungal infection is caused by a dermatophytic fungus that is *Microsporum canis*, *Microsporum gyseum*, *Microsporum audouinii*, *Trichophyton tonsurans*, *Trichophyton mentagrophytes*, *Epidermophyton floccosum*, *Trichophyton rubrum*, or *Pityrosporum ovale*.

Another specific method of the invention is the method of treating a mammal afflicted with a fungal or yeast infection comprising administering to the mammal an effective anti-fungal or anti-yeast amount of a compound of formula (I) or formula (II) wherein the fungal infection is caused by *Candida albicans* or *Candida guilliermoundi*.

Another specific method of the invention is the method of treating a mammal afflicted with a fungal or yeast infection comprising administering to the mammal an effective anti-fungal or anti-yeast amount of a compound of formula (I) or formula (II) wherein the fungal infection is caused by *Blastomyces dermatidis* or *Cryptococcus neoformans*.

Another specific method of the invention is the method of treating a mammal afflicted with a yeast infection comprising administering to the mammal an effective anti-yeast amount of a compound of formula (I) or formula (II) wherein the yeast infection is caused by *Pityrosporum ovale*.

Another specific method of the invention is the method of inhibiting or killing a fungus or yeast comprising contacting the fungus or yeast with an effective anti-fungal or anti-yeast amount of a triterpene of formula (I) or formula (II) wherein the fungus is a dermatophytic fungus.

Another specific method of the invention is the method of inhibiting or killing a yeast comprising contacting the fungus or yeast with an effective anti-fungal or anti-yeast amount of a compound of formula (I) or formula (II) wherein the fungus is a dermatophytic fungus that is *Microsporum canis*, *Microsporum gyseum*, *Microsporum audouinii*, *Trichophyton tonsurans*, *Trichophyton mentagrophytes*, *Epidermophyton floccosum*, *Trichophyton rubrum*, or *Pityrosporum ovale*.

Another specific method of the invention is the method of inhibiting or killing a yeast comprising contacting the fungus or yeast with an effective anti-fungal or anti-yeast amount of a compound of formula (I) or formula (II) wherein the fungus is *Candida albicans* or *Candida guilliermoundi*.

Another specific method of the invention is the method of inhibiting or killing a yeast comprising contacting the fungus or yeast with an effective anti-fungal or anti-yeast amount of a compound of formula (I) or formula (II) wherein the fungus is *Blastomyces dermatidis* or *Cryptococcus neoformans*.

Another specific method of the invention is the method of inhibiting or killing a yeast comprising contacting the fungus or yeast with an effective anti-yeast amount of a compound of formula (I) or formula (II) wherein the yeast is *Pityrosporum ovale*.

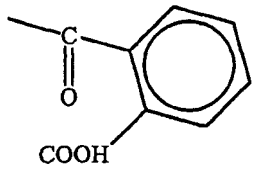
Another specific method of the invention is the method of inhibiting or killing a yeast comprising contacting the fungus or yeast with an effective anti-fungal or anti-yeast amount of a compound of formula (I) or formula (II) in vitro.

Another specific method of the invention is the method of inhibiting or killing a yeast comprising contacting the fungus or yeast with an effective anti-fungal or anti-yeast amount of a compound of formula (I) or formula (II) in vivo.

Specific triterpenes of formula (I) having anti-fungal or anti-yeast activity are shown in Table 1a and specific triterpenes of formula (II) having anti-fungal or anti-yeast activity are shown in Table 1b below.

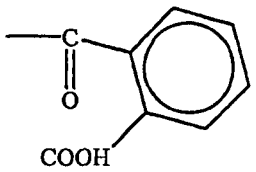
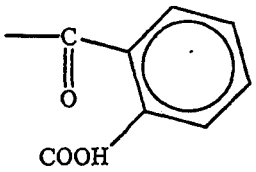
Table 1a. The R groups of compounds of formula (I) shown to have anti-fungal or anti-yeast activity.

Name	R_1	R_2	R_3	R_5	R_4	Active against
Betulin	H	-	$-CH_2OH$	-O-	H	Microsporum canis, Microsporum audouinii, Trichophyton rubrum
Betulin-3-maleate	H	-	$-CH_2OH$	-O-	$-C(=O)CH=CHCOOH$	Microsporum audouinii
Betulin-28-diglycolate	H	-	$-CH_2OC(=O)CH_2OCH_2COOH$	-O-	H	Microsporum canis
Betulin-28-glutarate	H	-	$-CH_2OC(=O)CH_2CH_2CH_2COOH$	-O-	H	Pityrosporum ovale, Trichophyton tonsurans, Trichophyton rubrum, Trichophyton mentagrophytes, Epidermophyton floccosum

Name	R_1	R_2	R_3	R_5	R_4	Active against
Betulin-28-maleate	H	-	$-CH_2OC(=O)CH=CHCOOH$	-O-	H	Microsporum canis
Betulin-28-phthalate	H	-		-O-	H	Microsporum canis, Microsporum audouinii, Trichophyton tonsurans, Trichophyton rubrum
Betulin-28-succinate	H	-	$-CH_2OC(=O)CH_2CH_2COOH$	-O-	H	Microsporum audouinii
Betulin-3,28-diglycine	H	-	$-CH_2OC(=O)CH_2NH_2$	-O-	$-C(=O)CH_2NH_2$	Microsporum canis
Betulin-3,28-didiglycolate	H	-	$-CH_2OC(=O)CH_2OCH_2COOH$	-O-	$-C(=O)CH_2OCH_2COOH$	Trichophyton mentagrophytes
Betulin-3,28-dimaleate	H	-	$-CH_2OC(=O)CH=CHCOOH$	-O-	$-C(=O)CH=CHCOOH$	Microsporum audouinii

Name	R_1	R_2	R_3	R_5	R_4	Active against
Betulin-3,28-di(3′,3′-dimethyl) glutarate	H	-	$-CH_2OC(=O)CH_2C-(CH_3)_2CH_2COOH$	-O-	$-CH_2OC(=O)CH_2C-(CH_3)_2CH_2COOH$	Microsporum canis, Microsporum audouinii, Microsporum gypseum, Trichophyton tonsurans, Trichophyton rubrum, Trichophyton mentagrophytes, Epidermophyton floccosum

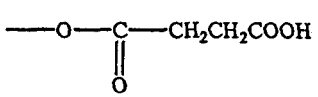
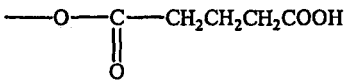
Name	R_1	R_2	R_3	R_5	R_4	Active against
Betulin-3,28-dioxalate-3,28-poly-ethyleneimine	H	-	$-CH_2OC(=O)C(=O)-(-NHCH_2CH_2-)_x-[-N(CH_2CH_2NH_2)CH_2CH_2-]_y$	-O-	$-C(=O)C(=O)-(-NHCH_2CH_2-)_x-[-N(CH_2CH_2NH_2)CH_2CH_2-]_y$	Candida albicans, Candida guilliermoundii, Blastomyces dermaidis, Crytococcus neoformans, Microsporum canis, Microsporum audouinii, Microsporum gypseum, Trichophyton tonsurans, Trichophyton mentagrophytes, Epidermophyton floccosum

Name	R_1	R_2	R_3	R_5	R_4	Active against
Betulin-3,28-diphthalate	H	-		-O-		Trichophyton tonsurans, Epidermophyton floccosum, Microsporum canis, Microsporum audouinii, Microsporum gypseum, Trichophyton mentagrophytes
Betulin-3,28-disuccinate	H	-	$-CH_2OC(=O)CH_2CH_2COOH$	-O-	$-C(=O)CH_2CH_2COOH$	Microsporum audouinii, Microsporum canis
Betulin-3,28-di-L-valine	H	-	$-CH_2OC(=O)-CH_2(NH_2)CH(CH_3)_2$	-O-	$-C(=O)-CH_2(NH_2)CH(CH_3)_2$	Trichophyton rubrum
Lupeol	H	-	$-CH_3$	-O-	H	Trichophyton mentagrophytes
Lupeol-3-amine	H	-	$-CH_3$	-	H	Trichophyton mentagrophytes

Name	R_1	R_2	R_3	R_5	R_4	Active against
Lupeol-3-(3',3', dimethyl) succinate	H	-	$-CH_3$	-O-	$-CH_2OC(=O)CH_2C(CH_3)_2COOH$	Trichophyton mentagrophytes
Lupeol-3-maleate	H	-	$-CH_3$	-O-	$-C(=O)CH=CHCOOH$	Trichophyton mentagrophytes
Lupenone	H	-	$-CH_3$	–	(=O)	Trichophyton mentagrophytes
Lupenon-1,2-ene-2-ol	H	-	$-CH_3$	–	(=O)	Trichophyton mentagrophytes

In addition, lupenon-1,2-ene-2-ol has a double bond between carbons 1 and 2. The other compounds in Table 1 have a single bond at that position.

Table 1b. The R groups of compounds of formula (II) shown to have antifungal activity.

Name	R_1	Active Against
Allobetulin	OH	Microsporum audouinii, Pityrosporum ovale
Allobetulin-3-succinate		Microsporum canis, Candida albicans, Microsporum audouinii, Trichophyton rubrum, Trichophyton mentagrophytes
Allobetulin-3-glutarate		Trichophyton tonsurans, Microsporum canis, Microsporum audouinii

Name	R_1	Active Against
Allobetulin-3-L-valine		Microsporum audouinii, Pityrosporum ovale

Processes for preparing compounds of the invention (i.e., compounds of formula (I) or formula (II)) are provided as further embodiments of the invention and are illustrated by the following procedures in which the meanings of the generic radicals are as given above unless otherwise qualified. Specifically, the compounds of formula (I) or formula (II) can be prepared from convenient starting materials, employing procedures (e.g., reagents and reaction conditions) known to those of skill in the art. For example, suitable reagents and reaction conditions are disclosed, e.g., in *Advanced Organic Chemistry, Part B: Reactions and Synthesis*, Second Edition, Carey and Sundberg (1983); *Advanced Organic Chemistry, Reactions, Mechanisms, and Structure,* Second Edition, March (1977); Greene, T.W., *Protecting Groups In Organic Synthesis*, Third Edition, 1999, New York, John Wiley & sons, Inc.; and *Comprehensive Organic Transformations*, Second Edition, Larock (1999). Additionally, specific exemplary procedures are shown in the examples herein below.

In cases where compounds are sufficiently basic or acidic to form stable nontoxic acid or base salts, administration of the compounds as salts may be appropriate. Examples of pharmaceutically acceptable salts are organic acid addition salts formed with acids which form a physiological acceptable anion, for example, tosylate, methanesulfonate, acetate, citrate, malonate, tartarate, succinate, benzoate, ascorbate, α-ketoglutarate, and α-glycerophosphate. Suitable inorganic salts may also be formed, including hydrochloride, sulfate, nitrate, bicarbonate, and carbonate salts.

Pharmaceutically acceptable salts may be obtained using standard procedures well known in the art, for example by reacting a sufficiently basic compound such as an amine with a suitable acid affording a physiologically acceptable anion. Alkali metal (for example, sodium, potassium or lithium) or alkaline earth metal (for example calcium) salts of carboxylic acids can also be made.

The compounds of formula (I) or (II) can be formulated as pharmaceutical compositions and administered to a mammalian host, such as a human patient in a variety of forms adapted to the chosen route of administration, i.e., orally or parenterally, by intravenous, intramuscular, topical or subcutaneous routes.

Thus, the present compounds may be systemically administered, e.g., orally, in combination with a pharmaceutically acceptable vehicle such as an inert diluent or an assimilable

edible carrier. They may be enclosed in hard or soft shell gelatin capsules, may be compressed into tablets, or may be incorporated directly with the food of the patient's diet. For oral therapeutic administration, the active compound may be combined with one or more excipients and used in the form of ingestible tablets, buccal tablets, troches, capsules, elixirs, suspensions, syrups, wafers, and the like. Such compositions and preparations should contain at least 0.1% of active compound. The percentage of the compositions and preparations may, of course, be varied and may conveniently be between about 2 to about 60% of the weight of a given unit dosage form. The amount of active compound in such therapeutically useful compositions is such that an effective dosage level will be obtained.

The tablets, troches, pills, capsules, and the like may also contain the following: binders such as gum tragacanth, acacia, corn starch or gelatin; excipients such as dicalcium phosphate; a disintegrating agent such as corn starch, potato starch, alginic acid and the like; a lubricant such as magnesium stearate; and a sweetening agent such as sucrose, fructose, lactose or aspartame or a flavoring agent such as peppermint, oil of wintergreen, or cherry flavoring may be added. When the unit dosage form is a capsule, it may contain, in addition to materials of the above type, a liquid carrier, such as a vegetable oil or a polyethylene glycol. Various other materials may be present as coatings or to otherwise modify the physical form of the solid unit dosage form. For instance, tablets, pills, or capsules may be coated with gelatin, wax, shellac or sugar and the like. A syrup or elixir may contain the active compound, sucrose or fructose as a sweetening agent, methyl and propylparabens as preservatives, a dye and flavoring such as cherry or orange flavor. Of course, any material used in preparing any unit dosage form should be pharmaceutically acceptable and substantially non-toxic in the amounts employed. In addition, the active compound may be incorporated into sustained-release preparations and devices.

The active compound may also be administered intravenously or intraperitoneally by infusion or injection. Solutions of the active compound or its salts can be prepared in water, optionally mixed with a nontoxic surfactant. Dispersions can also be prepared in glycerol, liquid polyethylene glycols, triacetin, and mixtures thereof and in oils. Under ordinary conditions of storage and use, these preparations contain a preservative to prevent the growth of microorganisms.

The pharmaceutical dosage forms suitable for injection or infusion can include sterile aqueous solutions or dispersions or sterile powders comprising the active ingredient which are adapted for the extemporaneous preparation of sterile injectable or infusible solutions or dispersions, optionally encapsulated in liposomes. In all cases, the ultimate dosage form should be sterile, fluid and stable under the conditions of manufacture and storage. The liquid carrier or vehicle can be a solvent or liquid dispersion medium comprising, for example, water, ethanol, a polyol (for example, glycerol, propylene glycol, liquid polyethylene glycols, and the like), vegetable oils, nontoxic glyceryl esters, and suitable mixtures thereof. The proper fluidity can be maintained, for example, by the formation of liposomes, by the maintenance of the required particle size in the case of dispersions or by the use of surfactants. The prevention of the action of microorganisms can be brought about by various antibacterial and antifungal agents, for example, parabens, chlorobutanol, phenol, sorbic acid, thimerosal, and the like. In many cases, it will be preferable to include isotonic agents, for example, sugars, buffers or sodium chloride. Prolonged absorption of the injectable compositions can be brought about by the use in the compositions of agents delaying absorption, for example, aluminum monostearate and gelatin.

Sterile injectable solutions are prepared by incorporating the active compound in the required amount in the appropriate solvent with various of the other ingredients enumerated above, as required, followed by filter sterilization. In the case of sterile powders for the preparation of sterile injectable solutions, the preferred methods of preparation are vacuum drying and the freeze drying techniques, which yield a powder of the active ingredient plus any additional desired ingredient present in the previously sterile-filtered solutions.

For topical administration, the present compounds may be applied in pure form, i.e., when they are liquids. However, it will generally be desirable to administer them to the skin as compositions or formulations, in combination with a dermatologically acceptable carrier, which may be a solid or a liquid.

Useful solid carriers include finely divided solids such as talc, clay, microcrystalline cellulose, silica, alumina and the like. Useful liquid carriers include water, alcohols or glycols or water-alcohol/glycol blends, in which the present compounds can be dissolved or dispersed at effective levels, optionally with the aid of non-toxic surfactants. Adjuvants such as fragrances and additional antimicrobial agents can be added to optimize the properties for a given use. The

resultant liquid compositions can be applied from absorbent pads, used to impregnate bandages and other dressings, or sprayed onto the affected area using pump-type or aerosol sprayers.

Thickeners such as synthetic polymers, fatty acids, fatty acid salts and esters, fatty alcohols, modified celluloses or modified mineral materials can also be employed with liquid carriers to form spreadable pastes, gels, ointments, soaps, and the like, for application directly to the skin of the user.

Examples of useful dermatological compositions which can be used to deliver the compounds of formula I to the skin are known to the art; for example, see Jacquet et al. (U.S. Pat. No. 4,608,392), Geria (U.S. Pat. No. 4,992,478), Smith et al. (U.S. Pat. No. 4,559,157) and Wortzman (U.S. Pat. No. 4,820,508).

Useful dosages of the compounds of formula I can be determined by comparing their *in vitro* activity, and *in vivo* activity in animal models. Methods for the extrapolation of effective dosages in mice, and other animals, to humans are known to the art; for example, see U.S. Pat. No. 4,938,949.

Generally, the concentration of the compound(s) of formula I in a liquid composition, such as a lotion, will be from about 0.1-25 wt-%, preferably from about 0.5-10 wt-%. The concentration in a semi-solid or solid composition such as a gel or a powder will be about 0.1-5 wt-%, preferably about 0.5-2.5 wt-%.

The amount of the compound, or an active salt or derivative thereof, required for use in treatment will vary not only with the particular salt selected but also with the route of administration, the nature of the condition being treated and the age and condition of the patient and will be ultimately at the discretion of the attendant physician or clinician.

In general, however, a suitable dose will be in the range of from about 0.5 to about 100 mg/kg, e.g., from about 10 to about 75 mg/kg of body weight per day, such as 3 to about 50 mg per kilogram body weight of the recipient per day, preferably in the range of 6 to 90 mg/kg/day, most preferably in the range of 15 to 60 mg/kg/day.

The compound is conveniently administered in unit dosage form; for example, containing 5 to 1000 mg, conveniently 10 to 750 mg, most conveniently, 50 to 500 mg of active ingredient per unit dosage form.

Ideally, the active ingredient should be administered to achieve peak plasma

concentrations of the active compound of from about 0.5 to about 75 μM, preferably, about 1 to 50 μM, most preferably, about 2 to about 30 μM. This may be achieved, for example, by the intravenous injection of a 0.05 to 5% solution of the active ingredient, optionally in saline, or orally administered as a bolus containing about 1-100 mg of the active ingredient. Desirable blood levels may be maintained by continuous infusion to provide about 0.01-5.0 mg/kg/hr or by intermittent infusions containing about 0.4-15 mg/kg of the active ingredient(s).

The desired dose may conveniently be presented in a single dose or as divided doses administered at appropriate intervals, for example, as two, three, four or more sub-doses per day. The sub-dose itself may be further divided, e.g., into a number of discrete loosely spaced administrations; such as multiple inhalations from an insufflator or by application of a plurality of drops into the eye.

The ability of a compound of the invention to act as an anti-fungal agent may be determined using pharmacological models which are well known to the art, including the tests described in the Examples below.

The compounds of the invention may be also be useful as pharmacological tools for the further investigation of the mechanism of their anti-fungal action.

The compounds of the invention can also be administered in combination with other therapeutic agents that are effective to treat fungal or yeast infections, or to inhibit or kill a fungus or yeast.

The system used to name the compounds of the invention will be clear to one of skill in the art based on the following examples. Names generally consist of the base structure, e.g., betulin, allobetulin, or lupeol, followed by a substituent. For example, betulin-28-succinate, with the structure shown in Example 1, consists of a succinic acid molecule esterified to the hydroxyl at carbon 28 of betulin. If no number is given for the substituent, the substituent is attached to the hydroxyl at carbon 3 on the base structure.

Betulin-3-glycerol oxalate is a compound of formula (I), wherein R_4 and R_5 together are hydrooxyl, R_2 and R_3 together are -OC(=O)C(=O)OCH$_2$CH(OH)CH$_2$OH, and R_1 is hydrogen. Betulin-1-ene-2-ol is a compound of formula (I), wherein the bond between carbons 1 and 2 is a double bond, R_1 is hydroxyl, R_2 and R_3 together are hydroxymethyl, and R_4 and R_5 together are oxo. Uvaol is a compound of formula (II), wherein R_{10} is methyl, R_9 is hydrogen, R_8 is methyl,

R_7 is hydrogen, R_{11} is hydroxymethyl, R_6 is absent and the bond between carbons 12 and 13 is double, R_3 is hydrogen, R_4 and R_5 are methyl, R_2 is hydrogen, and R_1 is hydroxy. Oleanolic acid has the same structure as uvaol, except it has a carboxy at R_{11} instead of hydroxymethyl. The structure of hederin hydrate is disclosed at page 871 of the Aldrich Chemical Co. 2000-2001 catalog. The structure of other named compounds can be found in standard sources such as the *Merck Index*. "Betulin arabinose galactan" refers to betulin in a solution of arabino-galactan.

Unless otherwise stated, amino acid substituents are attached to the compounds of the invention through their carboxyl groups via ester linkages. Thus, betulin-3,28-diglycine is the same compound as betulin-3,28-diglycine ester.

The invention will now be illustrated by the following non-limiting Examples.

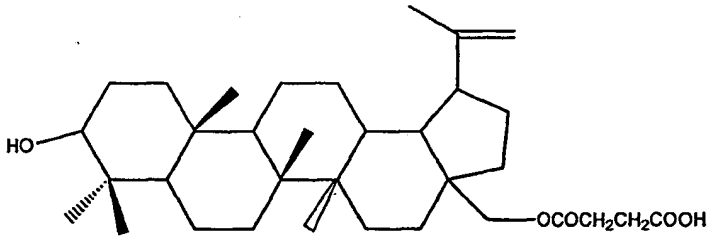
Synthesis

Synthesis of particular compounds of the present invention is disclosed in the following examples.

Examples

Example 1

Betulin-28-succinate



Betulin-28-succinate

m=0.200 g

$C_{34}H_{54}O_5$

Exact Mass: 542.40

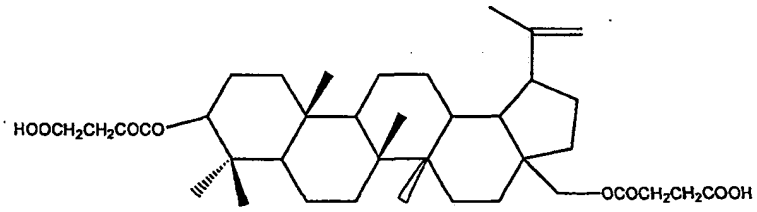
Mol. Wt.: 542.79

C, 75.23; H, 10.03; O, 14.74

Place Betulin 1.00 g (1 equivalent) along with Succinic anhydride 0.249 g (1.1 equivalent) and imidazole 0.462 g (3 equivalent) in a 25 ml flask. Add 20 ml dried dichloromethane, stir and reflux for 24 hours. After the reaction completes, add 10 ml 3% HCl, shake gently. The pH should be 2. Separate the organic part. Use dichloromethane (3x5 ml) to extract the water layer. Combine the organic part and use 3% HCl (2x10 ml) to wash it. Use Na_2SO_4 (anhy.) to dry the organic part. Evaporate the solvent, get white powder 1.10 g. Use small amount of acetone to tritrate the white product. After drying, get 0.90 g white granular solid with yield 73.2%. M.P.: 234.1-235.5°C; IR (KBr): 3355.76, 2953.19, 1734.29, 1708.63, 1264.63, 1174.11 cm^{-1}; ^1H NMR ($CDCl_3$): δ4.69 (S, 1H), 4.59 (S, 1H), 4.32 (D, J=11.1 Hz, 1H), 3.91 (D, J=11.1 Hz, 1H), 3.22 (M, 1H), 2.68 (M, 4H), 2.44 (M, 1H), 1.68 (S, 3H), 0.76, 0.82, 0.97, 1.02 (All S, 4x3H), 0.71-2.1 (complex, 28H); ^{13}C NMR ($CDCl_3$): 172.43, 167.96, 145.61, 105.38, 74.56, 58.71, 50.80, 45.88, 44.32, 43.21, 41.94, 38.21, 36.38, 34.36, 34.21, 33.12, 32.66, 30.01, 29.68, 25.23, 25.08, 24.57, 24.37, 23.50, 22.87, 22.54, 20.71, 16.30, 14.67, 13.79, 11.62, 11.54, 10.89, 10.30;

Example 2

Betulin-3,28-disuccinate



Betulin-3,28-disuccinate

m=0.200 g

$C_{38}H_{58}O_8$

Exact Mass: 642.41

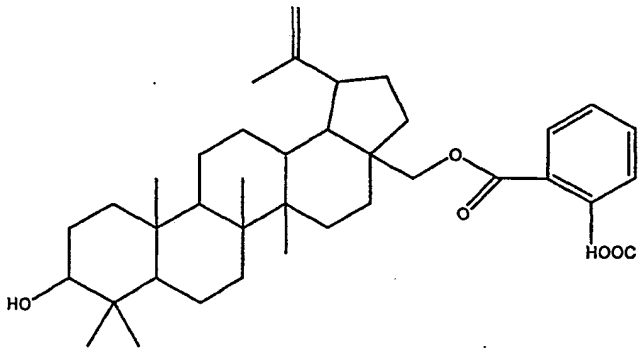
Mol Wt.: 642.86

C, 71.00; H, 9.09; O, 19.91

Place 0.5 g Betulin along with 0.34 g succinic anhydride and 0.46 g imidazole in a 25 ml flask. Add 15 ml CH_2Cl_2 (dried) and reflux for 12 hours. Add 10 ml 3% HCl, separate the organic part, use CH_2Cl_2 (3x5 ml) to wash, and combine the organic parts. Use 3% HCl (2x10 ml) wash the organic part, then use Na_2SO_4 to dry it. Evaporating the solvent gives 0.73 g yellow powder. Useing $CHCl_3$ - hexane to crystalize gives 0.65 g yellow powder. Or stiring the solid with 3% HCl in the warm condition for 12 hours, followed by filtration and drying, gives 0.60 g powder with yield 82.5%. M.P. (decomp.) 116.1-117.8°C; IR(KBr): 2954.83, 1726.44, 1169.46 cm^{-1}; ^1H NMR ($CDCl_3$): 4.69 (S, 1H), 4.59 (S, 1H), 4.51 (M, 1H), 4.31 (D, J=11.4Hz, 1H), 3.88 (D, J=10.8 Hz, 1H), 2.67 (M, 8H), 2.44 (M, 1H), 1.68 (S, 3H), 1.3, 0.98, 0.85, 0.86, 0.79 (all S, 5x3H), 1.06-2.1 (complex, 24H); ^{13}C NMR ($CDCl_3$): 173.73, 173.65, 167.98, 167.37, 145.63, 105.44, 77.09, 58.72, 50.91, 45.77, 44.30, 43.25, 41.94, 38.22, 36.40, 33.88, 33.36, 33.10, 32.56, 29.97, 29.61, 25.18, 24.87, 24.61, 23.41, 22.54, 20.67, 19.13, 16.34, 14.65, 13.69, 12.04, 11.68, 11.55, 1031;

Example 3

Betulin-28-phthalate



Betulin-28-phthalate

$C_{38}H_{54}O_5$

Exact Mass: 590.40

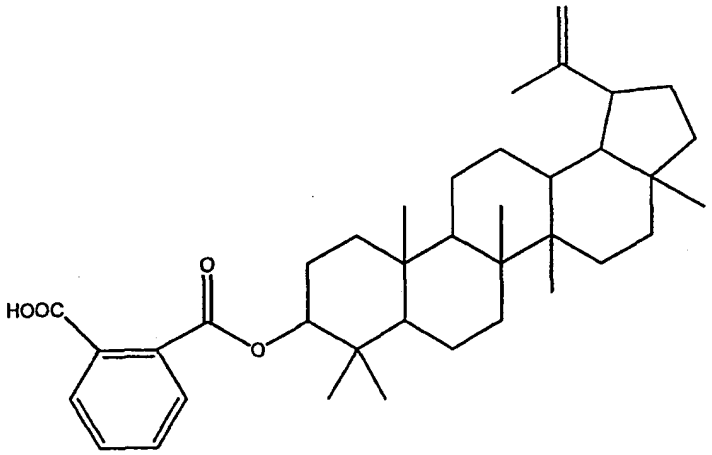
Mol. Wt.: 590.83

C, 77.25; H, 9.21; O, 13.54

Place Betulin 1 g (1 equivalent) and imidazole 0.31 g (4 equivalents) with phthalic anhydride 0.35 g (1.05 equivalents) in a 15 mL flask. Add 5 mL of 1-methyl-2-pyrrolidinone and stir at room temperature for 48 hours. Pour the mixture into the water with strong stirring and adjust pH around 3. Stir for 2-3 hours. All the chunks should become small particles. After filtration, use water to wash three times, and then dry it in the oven. Get 1.25 g white solid. Use ethyl acetate: Hexane (1:4) to elute the product from the silica gel column and get 0.69 g white prism solid. Yield is 51.5%. M.P.: 205.2-206.9°C. JR (cm^{-1}): 3500.0, 2957.0, 2876.4, 1719.7, 1458.2, 1386.5, 1289.8, 1136.8, 1072.4; ^1H NMR ($CDCl_3$, ppm): 7.93 (D, 1H, J=6.9Hz), 7.73 (D, 1H, J=6.6 Hz), 7.59 (M, 2H), 4.71 (S, 1H), 4.60 (S, 1H), 4.53 (D, 1H, J=8.4 Hz), 4.14 (D, 1H, J=10.8 Hz), 3.22 (M, 1H), 2.51 (M, 1H), 1.69 (S, 3H), 1.05, 0.97, 0.95, 0.82, 0.76 (all S, 5x3H), 2.2-0.6 (Complex, 26H); ^{13}C NMR ($CDCl_3$, ppm): 171.85, 169.03, 150.46, 133.90, 132.46, 131.13, 130.35, 129.19, 110.25, 79.43, 66.23, 64.90, 55.60, 50.69, 49.26, 48.08, 46.83, 43.07, 41.12, 39.18, 39.04, 38.01, 37.48, 34.92, 34.41, 30.11, 29.92, 28.34, 27.69, 27.37, 25.54, 21.14, 19.53, 18.58, 16.45, 16.38, 15.75, 15.61, 15.14.

Example 4

Lupeol-3-phthalate



Lupeol-3-phthalate

$C_{38}H_{54}O_4$

Exact Mass: 574.40

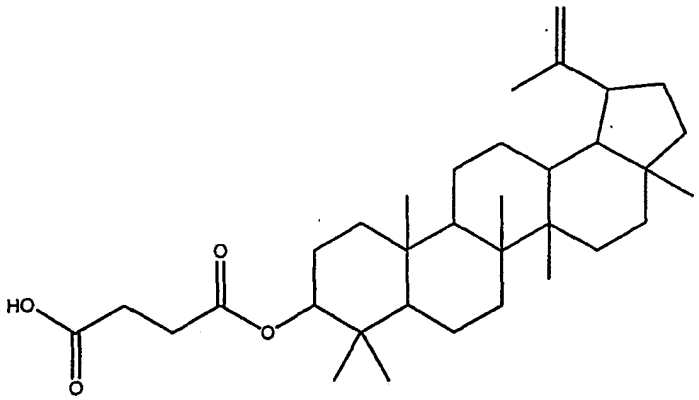
Mol. Wt.: 574.83

C, 79.40; H, 9.47; O, 11.13

Place Lupeol 0.100 g and imidazole 0.96 g with 0.069 g phthalic anhydride in a 25 mL flask, add dried dichloromethane 10 mL and reflux for 24 hours. Then use 3% HCl (3x5 mL) to wash the organic part, which is followed by drying with, sodium sulfate (anhy.). After evaporate the solvent, receive white powder, which is followed by stirring with 3% HCl for 12 hours. Then filter and dry the white solid in the oven. This results in 0.128 g white product with 94.8% yield. M.P.: 160.2-162.1°C. ^{1}H NMR ($CDCl_3$, ppm): 7.96 (D, 1H, J-6.9 Hz), 7.79 (D, 1H, J=6.0 Hz), 7.63 (M, 2H), 4.79 (M, 1H), 4.74 (S, 1H), 4.63 (S, 1H), 2.44 (M, 1H), 1.74 (S, 3H), 1.46, 1.08, 1.00, 0.93, 0.91, 0.84 (S, 6x3H), 2.1-0.7 (Complex, 25H). ^{13}C NMR ($CDCl_3$, ppm): 172.05, 168.19, 151.29, 133.74, 132.25, 131.23, 130.79, 130.35, 129.37, 109.73, 83.59, 55.91, 50.73, 48.67, 48.37, 43.37, 43.21, 41.24, 40.37, 38.81, 38.43, 37.48, 35.94, 34.59, 30.21, 28.40, 27.81, 25.47, 23.51, 21.35, 19.66, 18.56, 18.37, 16.99, 16.51, 16.35, 14.91.

Example 5

Lupeol-3-succinate



Lupeol-3-succinate

$C_{34}H_{54}O_4$

Exact Mass: 526.40

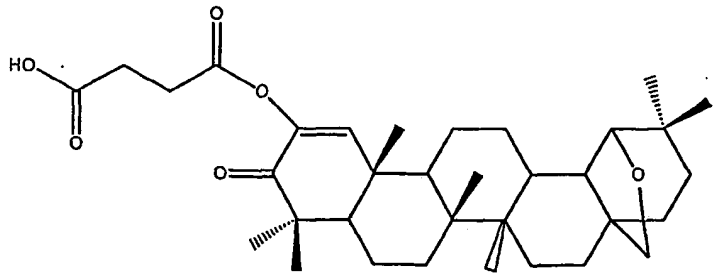
Mol. Wt.: 526.79

C, 77.52; H, 10.33; O, 12.15

Place Lupeol 100 mg (1 equivalence) and succinic anhydride 0.070 g (3 equivalence) with imidazole 0.016 g (1 equivalence) in a 25 mL flask. Add dried dichloromethane 10 mL, then reflux for 48 hours. After the reaction is done, add sodium bicarbonate saturated water solution 10 mL, separate the organic part, and extract the water phase with dichloromethane (3x5mL). Then use 3% HCl (3x10mL) to wash the organic part, which is followed by drying with sodium sulfate (anhy.). Evaporating the solvent gives a white powder, which is stirred with 3% HCl 15 mL overnight, which is followed by filtration and drying in the oven. 0.12 g white powder is obtained with 97.6% yield. M.P.: 224.7-226.3°C. ^{1}H NMR; 4.69 (S, 1H), 4.57 (S, 1H) 4.501 (M, 1H), 2.66 (M, 4H), 2.39 (M, 1H), 1.68 (S, 3H), 1.36, 1.03, 0.94, 0.85, 0.83, 0.79 (S, 6x3H), 1.8-0.7 (Complex, 25H), ^{13}C NMR ($CDCl_3$, ppm): 174.13, 168.54, 147.54, 105.94, 78.14, 51.94, 46.87, 44, 83, 44358, 39.56, 39.39, 37.40, 36.57, 34.91, 34.59, 34.41, 33.62, 32.13, 30.75, 26.39, 26.00, 25.72, 24.47, 23.99, 21.64, 20.21, 17.51, 15.86, 14.75, 14.58, 13.09, 12.74, 12.54, 11.09.

Example 6

3-Allobetulon-1-en-2-succinate



3-Allobetulon-1-en-2-succinate

$C_{34}H_{50}O_6$

Exact Mass: 554.36

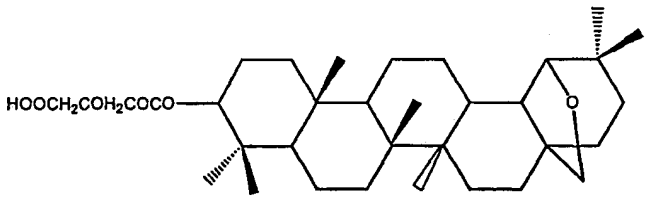
Mol. Wt.: 554.76

C, 73.61; H, 9.08; O, 17.30

Place 0.5 g 3-Allobetulon-1-en-2-ol (1 equivalent) and 0.33 g succinic anhydride (3 equivalents) with 0.13 g 4-(dimethylamino)-pyridine (1 equivalent) in a 25 mL flask. Add 10 mL acetonitrile and reflux for 48 hours, which is followed by adding 15 mL chloroform. Use 10 mL 3% HCl to wash the organic part three times, which is followed by drying with sodium sulfate (anhy.). Evaporating the solvent gives 0.55 g crude product. Use silica gel column to separate the crude product with solvent hexane: diethyl ether (3:1), which results in 0.303 g white amorphous solid with yield 49.7%. M.P.: 178.1-180.4°C. IR (cm^{-1}); 2944.6, 2866.3, 1764.8, 1695.4, 1139.5; ^1H NMR ($CDCl_3$, ppm): 6.83 (S, 1H) 3.80 (D, 1H, J=7.8 Hz), 3.59 (S 1H), 3.49 (D, 1H, J=7.8 Hz), 2.82 (M 4H), 1.19, 1.17, 1.13, 1.05, 0.91, 0.82 (all S, 6x3H), 1.8-0.8 (Complex, 23H); ^{13}C NMR ($CDCl_3$, ppm): 198.10, 176.47, 170.86, 145.43, 143.16, 88.23, 71.52, 53.44, 46.99, 45.82, 45.40, 41.82, 41.84, 41.37, 40.07, 36.98, 36.58, 34.57, 33.54, 33.00, 29.10, 28.89, 28.79, 28.21, 26.66, 26.51, 24.89, 21.67, 20.52, 19.26, 16.49, 13.74.

Example 7

Allobetulin-3-diglycolate



Allobetulin-3-diglycolate

m=0.300 g

$C_{34}H_{54}O_6$

Exact Mass: 558.39

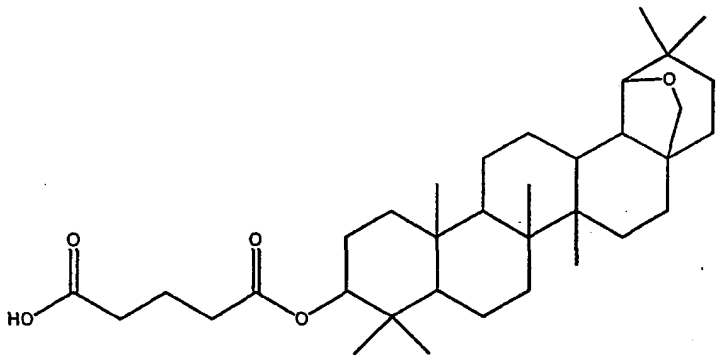
Mol. Wt.: 558.79

C, 73.08; H, 9.74; O, 17.18

In 25-mL flask, stir diglycolic anhydride 0.39 g and 0.5 g allobetulin in 15 mL $CHCl_3$. Then reflux for 24 hours. Add 10 mL saturated $NaHCO_3$, shake gently. Then separate the organic part, use the $CHCl_3$ (2x5 ml) to wash, and combine the organic parts. Use 3% HCl (10 ml) and water (2x10 ml) to wash it. Then use Na_2SO_4 (anhy.) to dry the organic part. Evaporating the solvent yields 0.57 g of white granular solid with yield 90.2%. M.P.: 285.2 (decompose). IR (KBr): 2964.07, 1753.33, 1223.67, 1110.16 cm^{-1}; ^1H NMR ($CDCl_3$); δ 4.64 (DD, 1H), 4.32 (S, 4H), 3.66 (D, 1H, J=9 Hz), 3.54 (S, 1H), 3.46 (D, 1H, J=9 Hz), 0.97, 0.926, 0.891, 0.866, 0.852, 0.828, 0.796 (all S, 7x3H), 1.1-1.9 (complex CH-, CH_2, 24H); ^{13}C NMR ($CDCl_3$): δ 171.28, 88.342, 83.431, 71.597, 69.498, 55.872, 51.339, 47.164, 41.837, 41.094, 40.985, 38.886, 38.289, 37.509, 37.079, 36.627, 34.478, 34.157, 33.057, 29.166, 28.408, 26.775, 26.601, 24.917, 24.072, 21.391, 18.476, 16.916, 16.064, 13.87.

Example 8

Allobetulin-3-glutarate



Allobetulin-3-glutarate

$C_{35}H_{56}O_5$

Exact Mass: 556.41

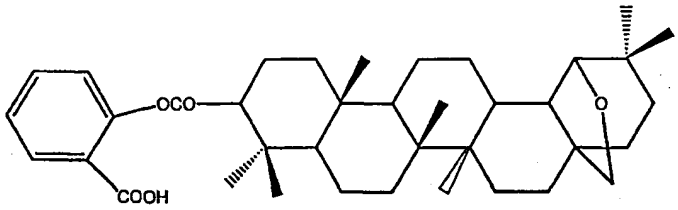
Mol. Wt.: 556.82

C, 75.50; H, 10.14; O, 14.37

Place 1 g Allobetulin (1 equivalent) and 0.52 g glutaric anhydride (2 equivalents) with imidazole 0.92 g (6 equivalence) in a 15 mL flask. Add 4.5 mL 1-methyl-2-pyrrolidinone and stir for 48 hours at 70°C. Pour the reaction mixture into 150 mL water. Adjust the pH to around 2. Stir for 3-4 hours and all the chunks should be broken into small particles. After filtration, dry the crude product in the oven. Crystalizing the crude product with chloroform and hexane yields 1.11 g of white amorphous product with yield 88.1%. M.P.: 283.2-284.9°C. IR (cm^{-1}): 2948.9, 1724.7, 1458.9, 1281.8, 1217.4; ^1H NMR ($CDCl_3$, ppm): 4.50 (M, 1H), 3.80 (D, 1H, J=8.1 Hz), 3.55 (S, 1H), 3.46 (D, 1H, J=7.8 Hz), 2.46 (M, 4H), 1.99 (M, 2H), 0.98, 0.93, 0.92, 0.87, 0.84, 0.80 (all S, 6x3H), 1.8-0.8 (Complex, 28H); ^{13}C NMR ($CDCl_3$, ppm): 177.86, 173.08, 88.34, 81.44, 71.60, 55.92, 51.35, 47.18, 41.84, 41.09, 40.99, 38.93, 38.22, 37.53, 37.09, 36.63, 34.49, 34.20, 34.06, 33.31, 33.06, 29.17, 28.36, 26.79, 26.62, 24.92, 24.10, 21.38, 20.43, 18.51, 16.95, 16.07, 13.87.

Example 9

Allobetulin-3-phthalate



Allobetulin-3-phthalate

m=0.300 g

$C_{38}H_{54}O_5$

Exact Mass: 590.40

Mol. Wt.: 590.83

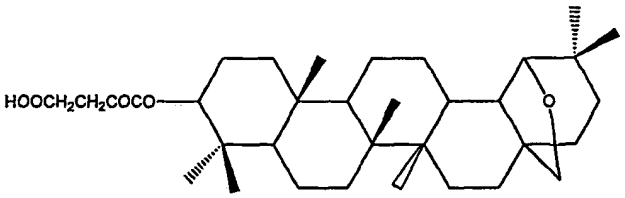
C, 77.25; H, 9.21; O, 13.54

In 25-ml flask, stir phthalic anhydride 0.20 g and imidazole 0.38 g in 10 ml CH_2Cl_2, add the 0.5 g Allobetulin into the flask, and then reflux for 6 hours. Add 10 ml saturated sodium bicarbonate

water solution into the flask, dissolve the solid, separate the organic part, use the CH_2Cl_2 (3x5 ml) wash and combine the organic parts. Use 3% HCl (3x10 ml) wash again. Use Na_2SO_4 (anhy.) to dry the organic part. Evaporate the solvent, get white solid 0.60 g with yield 89.6%. M.P.: 252.3-253.9°C; IR (KBr): 2948.90, 2868.36, 1724.74, 1660.31, 1458.97, 1289.84, 1136.82, 1072.39, 975.75 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.91 (D, J=6.6 Hz, 1H), 7.73 (D, J=6.9 Hz, 1H), 7.58 (M, 2H), 4.78 (M, 1H), 3.80 (D, 1H, J=7.8 Hz), 3.62 (S, 1H), 3.48 (D, J=7.8 Hz, 1H), 2.0-0.8 (complex, 45H); ^{13}C NMR ($CDCl_3$): 166.47, 163.55, 129.22, 127.32, 126.21, 125.98, 125.44, 124.28, 83.47, 78.42, 66.75, 51.23, 46.53, 42.31, 37.02, 36.25, 36.16, 34.15, 33.60, 32.72, 32.24, 31.77, 29.66, 29.37, 28.24, 24.31, 23.57, 21.96, 21.77, 20.08, 18.62, 16.60, 13.67, 12.19, 12.12, 11.26, 9.06.

Example 10

Allobetulin-3-succinate



Allobetulin-3-succinate

m=0.300 g

$C_{34}H_{54}O_5$

Exact Mass: 542.40

Mol. Wt.: 542.79

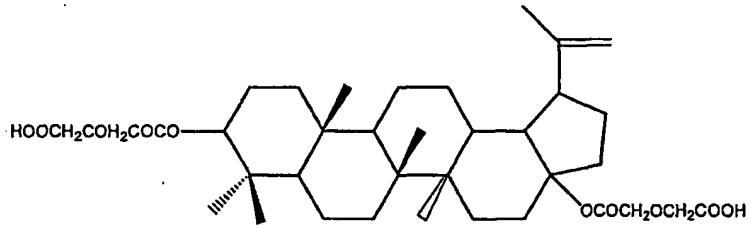
C, 75.23; H, 10.03; O, 14.74

In 25-ml flask, stir succinic anhydride 0.23 g and imidazole 0.46 g in 15 ml CH_2Cl_2, add 0.5 g allobetulin into the flask, and then reflux for 24 hours. Add 10 ml saturated sodium bicarbonate to dissolve the solid, then separate the organic part, use CH_2Cl_2 (2x5 ml) to wash and combine the organic parts. Use 3% HCl (2x10 ml) to wash the organic part. Use Sodium sulfate (anhy.)

to dry the organic part. Evaporating the solvent results in a white granular solid. Stir the crude product in 3% HCl for 12 hours, after filtration, which gives 0.48 g of a white solid, with yield 78.7%. M.P.: (decomp.) 258.1-259.5°C; IR (KBr): 2940.85, 2868.36, 1732.79, 1450.91, 1386.49, 1225.41, 1169.04 cm^{-1}; ^1H NMR ($CDCl_3$): δ 4.52 (M, 1H), 3.78 (D, J=7.5 Hz, 1H), 3.55 (S, 1H), 3.45 (D, J=7.5 Hz, 1H), 2.65 (M, 4H), 0.76, 0.78, 0.84, 0.86, 0.90, 0.92, 1.0 (all S, 7x3H), 1.1-1.9 (complex, 24H); ^{13}C NMR ($CDCl_3$): 172.78, 167.44, 83.50, 77.00, 66.73, 51.10, 46.50, 42.31, 36.99, 36.14, 34.08, 33.38, 32.67, 32.23, 31.77, 29.62, 29.35, 28.21, 24.93, 24.56, 24.32, 23.41, 21.94, 21.76, 20.08, 19.14, 16.54, 13.65, 12.07, 11.22, 9.04.

Example 11

Betulin-3,28-didiglycolate



Betulin-3,28-didiglycolate

m=0.200g

$C_{38}H_{58}O_{10}$

Exact Mass: 674.40

Mol. Wt.: 674.86

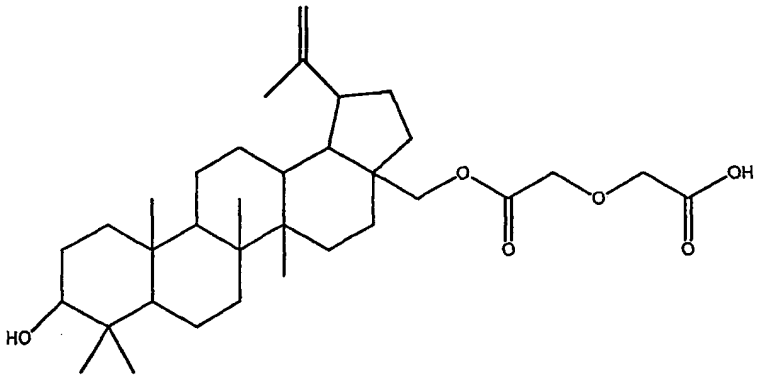
C, 67.63; H, 8.66; O, 23.71

In 15-ml flask, stir diglycolic anhydride 0.78 g and imidazole 0.92 g in 4.5ml 1-methyl-2-pyrrolidinone at 70°C. After they dissolve add 1 g Betulin. Stir for 24 hours. Pour mixture slowly into 180 ml water, adjust the pH to 2, stir the water solution until all the precipitate forms small granules. After the filtration, use 1% HCI, water to wash the product. Drying gives 1.45 g

granular product (little brown color) with yield 94.8%. M.P. (decomp.) 137.8-139.2°C; IR (KBr): 2961.07, 1747.02, 1220.45, 1144.87 cm^{-1}, ^1H NMR ($CDCl_3$): δ 4.71 (S, 1H), 4.61 (complex, 2H), 4.2-4.45 (complex, 9H), 3.96 (D, J-11.4 Hz), 2.45 (M, 1H), 1.70 (S, 3H), 0.83, 0.85, 0.97, 1.04, (S, 4×3H), 1.05-2.10 (complex, 28H); ^{13}C NMR ($CDCl_3$): 168.46, 168.29, 166.50, 166.17, 145.34, 105.65, 78.48, 64.66, 64.39, 64.28, 59.60, 50.83, 45.75, 44.28, 43.20, 41.94, 38.23, 36.40, 33.83, 33.43, 33.14, 32.56, 29.99, 29.58, 25.16, 23.57, 22.52, 20.61, 19.23, 16.31, 14.62, 13.66, 12.02, 11.68, 11.54, 10.27.

Example 12

Betulin-28-diglycolate



Betulin-28-diglycolate

$C_{37}H_{54}O_6$

Exact Mass: 558.39

Mol. Wt.: 558.79

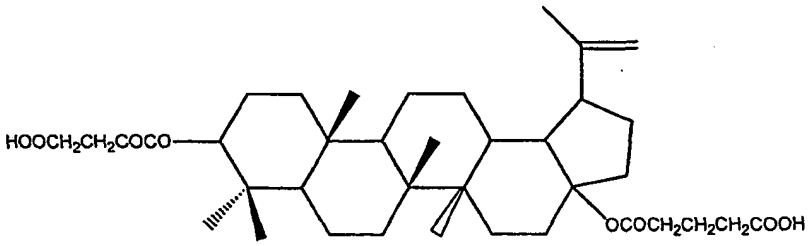
C, 73.08; H, 9.74; O, 17.18

Place Betulin 0.5 g (1 equivalent) and diglycolic anhydride 0.14 g (1.02 equivalents) with imidazole 0.31 g (4 equivalents) in a 15 mL flask. Add 4 mL 1-methyl-2-pyrrolidinone and stir 48 hours at room temperature. Pour the mixture into 150 mL water, which is followed by

adjusting pH to around 2. Stir for 2-3 hours. All the chunks should be broken to small particles. After filtration, dry the crude product in the oven, which is followed by passing through a silica gel column with hexane: diethyl ether (3:1). This yielded 0.43 g white prizm solid with yield 68.3%. M.P.: 219.2-220.2°C. IR (cm^{-1}): 3454.5, 2941.1, 1759.5, 1729.44, 1216.3, 1136.8, ^1H NMR ($CDCl_3$, ppm): 4.74 (S, 1H), 4.65 (S, 1H), 4.48 (D, 1H, J=11.1 Hz), 4.33 (S, 4h), 4.05 (D, 1H, J=11.1 Hz), 3.27 (M, 1H), 2.49 (M, 1H), 1.73 (S, 3H), 1.08, 1.02, 1.01, 0.87, 0.81 (all S, 5×3H), 2.2-0.6 (Complex, 25H); ^{13}C NMR ($CDCl_3$, ppm): 172.16, 171.55, 150.19, 110.46, 79.44, 69.60, 69.32, 64.58, 55.64, 50.69, 49.15, 48.02, 46.79, 43.06, 41.23, 39.21, 39.05, 38.01, 37.50, 34.83, 34.53, 30.01, 29.82, 28.34, 27.68, 27.36, 25.52, 21.11, 19.49, 18.64, 16.47, 16.39, 15.74, 15.14.

Example 13

Betulin-3,28-diglutarate



Betulin-3,28-diglutarate

m=0.300 g

$C_{40}H_{62}O_8$

Exact Mass: 670.44

Mol. Wt.: 670.92

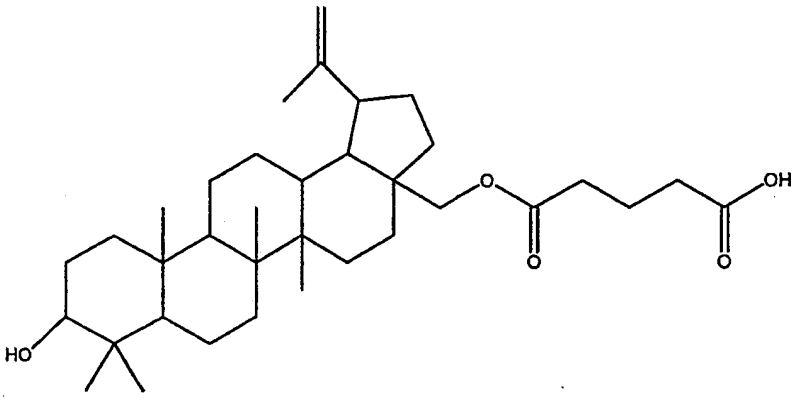
C, 71.61; H, 9.31; O, 19.08

In 15-ml flask, stir glutaric anhydride 1.29 g and imidazole 1.54 g in 4.5 ml 1-methyl-2-pyrrolidinone at 70°C. After they dissolve add 1g betulin. Stir for 48 hours. Pour mixture slowly into 180 ml water, adjust the pH to 2, and stir the water solution until all the precipitate

forms small granules. After the filtration, use 1% HCl in water to wash the product. Drying results in 1.22 g gray solid powder with yield 80.3%. M.P. (decomp.): 104.5-106.2°C; IR (KBr): 2956.95, 2876.42, 1732.79, 1458.97, 1386.49, 1201.25, 991.85 cm^{-1}; ^1H NMR ($CDCl_3$): δ 4.69 (S, 1H), 4.49 (S,1H), 4.50 (M, 1H), 4.29 (D, 1H, J=10.5 Hz), 3.85 (D, 1H, J=11.1 Hz), 2.42 (M, 9H), 1.98 (M, 5H),1.68 (S, 3H), 0.75-1.9 (complex, 39H); ^{13}C NMR ($CDCl_3$): 178.947, 173.693, 173.059, 150.463, 110.297, 81.478, 63.217, 55.712, 50.618, 49.132, 48.082, 46.741, 43.054, 41.247, 38.711, 38.194, 37.924, 37.414, 34.937, 34.449, 34.026, 33.669, 33.370, 30.120, 29.916, 28.371, 27.388, 25.493, 24.087, 21.157, 20.385, 20.254, 19.481, 18.519, 16.938, 16.516, 16.392, 15.109.

Example 14

Betulin-28-glutarate



Betulin-28-glutarate

$C_{35}H_{56}O_5$

Exact Mass: 556.41

Mol Wt.: 556.82

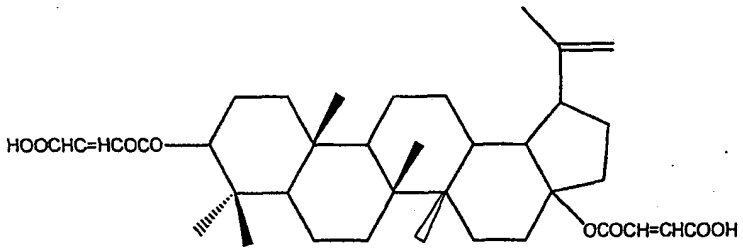
C, 75.50; H, 10.14; O, 14.37

Place 1 g of Betulin (1 equivalent) and 0.271 g glutaric anhydride (1.05 equivalents) with 0.615 g imidazole (4 equivalents) in a 25 mL flask, add 4 mL 1-methyl-2-pyrrolidinone and stir for 48

hours at room temperature. Pour the mixture in 150 mL water, while stirring. Then adjust pH to around 3. Break the big chunks to small particles, which is followed by filtration and drying in the oven. The crude products are passed through the silica gel column with diethyl ether: hexane (1:3). This results in 0.765 g white prism solid with a yield of 60.7%. M.P.: 204.3-206.1°C. IR (cm^{-1}): 3438.7, 2962.4, 2870.5, 1741.7, 1717.1, 1463.0, 1395.2; ^1H NMR ($CDCl_3$, ppm): 4.73 (S, 1H), 4.64 (S, 1H), 4.35 (D, 1H, J=11.1 Hz), 3.93 (D, 1H, J=11.1 Hz), 3.25 (M, 1H), 2.50 (M, 5H), 1.73 (S, 3H), 1.08, 1.02, 0.87, 0.81 (all S, 4×3H), 2.2-0.8 (Complex, 30H); ^{13}C NMR ($CDCl_3$, ppm): 177.72, 173.67, 150.49, 110.25, 79.39, 63.202, 55.65, 50.72, 49.15, 48.06, 46.75, 43.06, 41.23, 39.22, 39.05, 37.94, 37.51, 34.94, 33.68, 33.16, 30.14, 29.94, 28.35, 27.73, 27.40, 25.55, 21.14, 20.27, 19.51, 18.65, 16.47, 16.40, 15.74, 15.14.

Example 15

Betulin-3,28-dimaleate



Betulin-3,28-dimaleate

m=0.300g

$C_{38}H_{54}O_8$

Exact Mass: 638.38

Mol. Wt.: 638.83

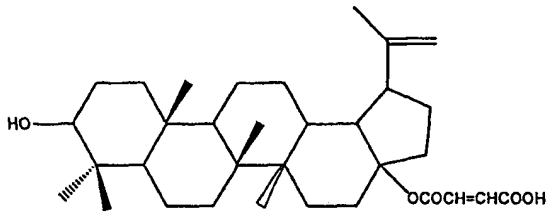
C, 71.44; H, 8.52; O, 20.04

In 50-ml flask, stir maleic anhydride 11.09 g and Betulin 5g in 20 ml 1-methyl-2-pyrrolidinone at 70°C for 48 hours. Pour the mixture slowly into 800 ml water, adjust the pH to 3, and stir the water solution until all the precipitation forms small granules. After the filtration, use 1% HCl,

in water to wash the product. Drying gives 6.50 g gray solid granules with yield 90.1%. M.P.: 181.4-182.9°C; IR (KBr): 2952.27, 1738.94, 1700.43, 1635.34, 1239.03, 994, 826 cm^{-1}; ^1H NMR ($CDCl_3$): 6.55-6.40 (M, 4H), 4.76-4.67 (complex, 3H), 4.56 (D, J=11.1 Hz, 1H), 4.09 (D, J=10.5 Hz, 1H), 2.45 (M, 1H), 1.70 (S, 3H), 0.78, 0.81, 0.90, 1.02, 1.10 (all S, 5x3H), 1.12-2.1 (complex, 24H); ^{13}C NMR ($CDCl_3$): 163.80, 163.41, 159.92, 159.76,145.10, 132.64, 132.20, 125.13, 124.76, 105.80, 80.56, 61.43, 50.83, 45.73, 44.30, 43.19, 41.94, 38.26, 36.40, 34.38, 33.80, 33.45, 33.23, 32.57, 29.90, 29.55, 25.04, 24.92, 23.50, 22.48, 20.59, 18.89, 16.30, 14.63, 13.63, 11.97, 11.68, 11.55, 10.90, 10.30.

Example 16

Betulin-28-maleate



Betulin-28-maleate

m=0.300g

$C_{34}H_{52}O_5$

Exact Mass: 540.38

Mol. Wt.: 540.77

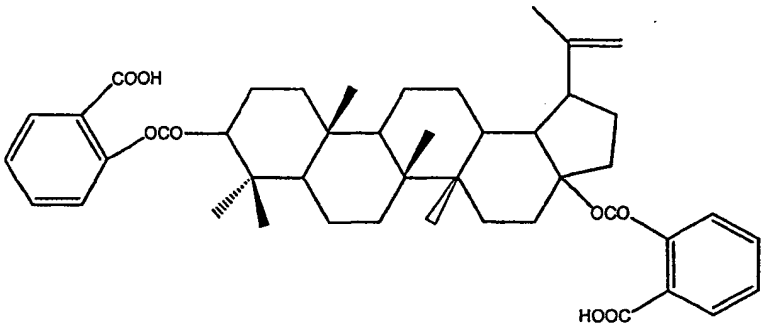
C, 75.51; H, 9.69; O, 14.79

In 500-ml flask, stir maleic anhydride 3.33 g and 10 g Betulin in 200 ml $CHCl_3$. Reflux for 40 hours. Add 50 mL 3% HCl, separate the organic part, use $CHCl_3$ (3x20 mL) to wash the aqueous phase, and combine the organic parts. Use 3% HCl (2x50 mL) to wash the organic phase, which is followed by using Na_2SO_4 (anhydrous) to dry organic part. After evaporating the solvent, use THF-hexane to crystalize the crude product. This gives 9.2 g white product with

yield 75.2%, M.P.: 242.5-243.6°C; IR (KBr): 3416.01, 2948.90, 2868.36, 1716.69, 1652.26, 1265.68, 1233.47 cm^{-1}; ^1H NMR($CDCl_3$): δ 6.5 (Q, 2H), 4.78 (S, 1H), 4.68 (S, 1H), 4.56 (D, J=11.1 Hz, 1H), 4.12 (D, J=11.1 Hz, 1H), 3.26 (M, 1H), 2.50 (M, 1H), 1.76 (S, 3H), 0.84, 0.90, 1.05, 1.06, 1.10 (S, 5x3H), 2.1-0.8 (complex, 25H); ^{13}C NMR ($CDCl_3$): 163.901, 159.57, 145.15, 132.58, 124.62, 105.75, 74.52, 61.44, 50.81, 45.85, 44.35, 43.18, 41.96, 38.25, 36.40, 34.39, 34.23, 33.27, 32.67, 29.91, 29.69, 25.09, 24.94, 23.51, 22.88, 22.50, 20.68, 16.27, 14.65, 13.80, 11.64, 11.56, 10.90, 10.33.

Example 17

Betulin-3,28-diphthalate



Betulin-3,28-diphthalate

m=0.300g

$C_{46}H_{58}O_8$

Exact Mass: 738.41

Mol. Wt.: 738.95

C, 74.77; H, 7.91; O, 17.32

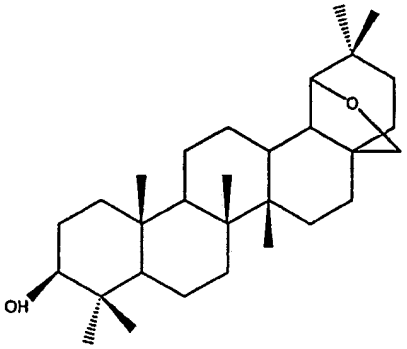
In 50-ml flask, stir phthalic anhydride 8.37 g and imidazole 7.69 g in 20 ml 1-methyl-1-pyrrolidinone at 70°C. After they dissolve, add 5g betulin. Stir for 48 hours. Pour mixture slowly into 800 ml water, adjust the pH to 2, and stir the water solution until all the precipitate forms small granules. After the filtration, use 1% HCl in water to wash the product. Drying

gives 7.59 g granules (light yellow color) with yield 90.8%. M.P. (decomp.) 166.8-168.6°C; IR (KBr): 2956.95, 2876.42, 1716.69, 1394.54, 1281.79, 1128.77, 1088.50, 991.85, 742.19 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.87 (M 2H), 7.77 (M, 2H), 7.58 (M, 4H), 4.76-4.53 (complex, 4H), 4.08 (D, J=10.2 Hz, 1H), 2.50 (M, 1H), 1.68 (S, 3H), 0.82, 0.84, 0.90, 1.02, 1.08 (all S, 5x3H), 1.1-2.2 (complex, 24H); ^{13}C NMR ($CDCl_3$): 168.57, 168.33, 163.68, 162.99, 145.58, 128.79, 128.23, 127.37, 126.56, 126.39, 126.32, 126.19, 125.22, 125.08, 124.69, 124.50, 105.47, 78.49, 60.12, 51.04, 45.80, 44.46, 43.36, 42.09, 39.22, 38.27, 36.40, 33.99, 33.56, 33.24, 32.62, 29.96, 29.53, 25.12, 23.55, 22.58, 20.68, 18.72, 16.42, 14.62, 13.66, 12.20, 11.72, 11.56, 10.48.

Example 18

Allobetulin,

oleanan-3β-ol-28,19-β-ether



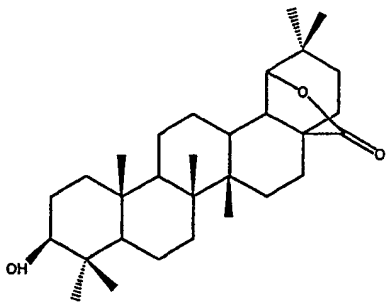
In 100-ml flask stir 2 g of Betulin in 50 ml of CH_2Cl_2 at 0°C. Add 5 ml of 99% CF_3COOH and stir for 30 minutes. Pour reaction mixture in 100 ml of cracked ice and separate the organic part. Extract with CH_2Cl_2 (3x10 ml) and wash combined organic extracts with conc. $NaHCO_3$ (2x20 ml) and water (2x20 ml), and dry the extract over Na_2SO_4 (anh.). Evaporation of solvent gives 1.98 g of Allobetulin, which was recrystallized from hexane-dichloromethane to yield white needles mp. 268-269°C [lit. 265-268], IR (KBr) 3448.5, 2941.5, 2866.6, 1780.7, 1456.6, 1384.4, 1168.9, 1035.0, cm^{-1}; ^1H NMR ($CDCl_3$) d 3.75 (D, J=10.3 Hz, 1H, 28-H), 3.51 (S, 1-H, 19-H), 3.41 (D, J=10.3 Hz, 1H, 28-H), 3.18 (DD, 1H, 3-H), 0.74, 0.76, 0.81, 0.88, 0.89, 0.94, 0.94 (all S, 7x3H, 27-, 23-, 24-, 25-, 26-, 29-, 30-Me), 1.01-1.74 (complex CH-, CH_2, 25 H,); ^{13}C NMR ($CDCl_3$) d 88.41, 79.38, 71.49, 55.77, 51.35, 47.07, 41.78, 40.99, 40.88, 40.87, 39.16,

37.52, 36.95, 36.51, 34.40, 34.18, 32.96, 29.08, 28.27, 27.57, 26.72, 26.72, 26.50, 24.82, 21.26, 18.54, 16.79, 15.96, 15.72, 13.82; MS (EI) 442, 424, 411, 371, 355, 303, 273, 257, 245, 231, 220, 207, 203, 189, 177, 162, 149, 135, 121, 107.

Example 19

Allobetulinlactone

oleanan-3β-ol-28,19-β-lactone

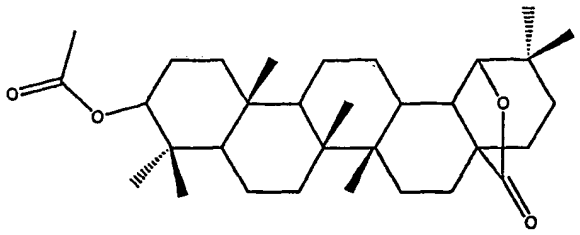


In 100-ml flask boil 2 g of Allobetulin-3-trifluoroacetyl lactone in 50 ml of CH_3OH in presence of 0.723 g KOH for 4 hours. Evaporate methanol and dilute with 100 mL of cold water. Filter the precipitate and wash with water (3x50 mL). Dry crystals in oven at 110°C and recrystallize from hexane-dichloromethane to yield white needles. mp. 316.3-317.6°C, IR (KBr) 3495, 2940, 2866, 1759, 1447, 1388, 1153, 1118, 967, 923 cm^{-1}; ^1H NMR ($CDCl_3$) d 3.97 (S, 1H, 19H), 3.22 (DD, 1H, 3H), 1.057, 1.000, 0.987, 0.942, 0.903, 0.87, 0.791 (all S, 7x3H, 23-, 24-, 25-, 26-, 27-, 29–, 30-Me), 1.1-1.9 (complex CH-, CH_2-, 24H); ^{13}C NMR ($CDCl_3$) d 180.207, 86.316, 79.174, 55.791, 51.528, 47.01, 46.413, 40.853, 40.212, 39.242, 39.177, 37.552, 36.313, 34.018, 33.843, 32.619, 32.232, 29.055, 28.254, 28.188, 27.642, 26.826, 25.842, 24.261, 21.178, 18.46, 16.85, 15.822, 15.669, 13.964; MS (EI) 456, 438, 423, 395, 356, 329, 261, 234, 206, 189, 175, 161, 147, 135, 121, 107, 95, 81, 69, 55, 43.

Example 20

Allobetulinlactone-3-acetate

oleanan-28,19-β-lactone-3-acetate

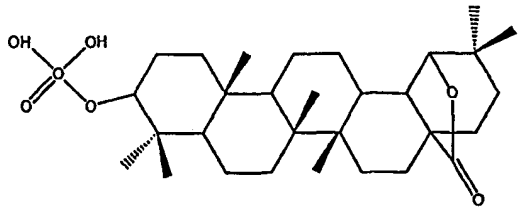


In 100-ml flask stir 2 g of 3-O-acetyl-betulin in 50 ml of CH_2Cl_2 at 0°C. Add 10 ml of 99% proof CF_3COOH stir for 10 minutes and after that add 2.2 g of powdered $NaBrO_3$. Stir the mixture for 6 hours and then pour in 100 ml of cracked ice and separate organic part. Extract with CH_2Cl_2 (3x10 ml) and wash combined organic extracts with 10% aqueous $NaHSO_3$ (2x30 ml), 5% aqueous $NaHCO_3$ (2x30 ml) and water (2x20 ml), and dry the extract over Na_2SO_4 (anh.). Evaporation of solvent gives 2.08 g of 3-O-acetyl allobetulin-lactone, which was recrystallized from hexane-dichloromethane to yield white needles. mp. 312.5-315.4°C (dec.), IR (KBr) 2943, 2878, 1761, 1729, 1502, 1486, 1446, 1374, 1252 cm^{-1}; ^1H NMR ($CDCl_3$) d 4.50 (DD, 1H, 3H), 3.94 (S, 1H, 19H), 2.03 (S, 3H, Ac-Me), 1.04, 0.97, 0.95, 0.8, 0.8, 0.79, 0.78 (all S, 7x3H, 23-, 24-, 24-, 25-, 26-, 29-, 30-Me), 1.02-1.79 (complex CH-, CH_2-, 23H); ^{13}C NMR ($CDCl_3$) d 13.899, 15.779, 16.741, 16.879, 18.307, 21.164, 21.601, 23.896, 24.210, 26.745, 25.784, 28.158, 28.159, 29.004, 32.181, 32.568, 33.792, 33.916, 36.284, 37.428, 38.055, 38.878, 40.175, 46.420, 40.831, 46.959, 51.419, 55.835, 180.352, 81.244, 86.381, 171.579; MS (EI) 482, 438, 424, 395, 356, 327, 281, 253, 207, 189, 174, 162, 147, 135, 121, 43.

Example 21

Allobetulinlactone-3-phosphate

oleanan-28,19-β-lactone-3-phosphate

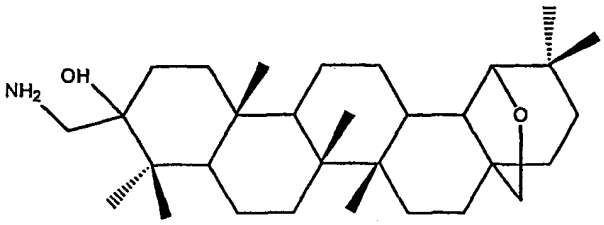


In 100 mL round bottom flask boil a solution of allobetulin-3-phosphodichloride in 50 mL of dioxane and 1 mL of water for 18 hours. Dilute with cold water (50 mL) and filter white precipitate. Wash on filter with water (3x30 mL). Dry in oven (temperature not higher than 110°C) to give 3.12 g of white crystalline compound mp. 226.7-230.1°C (dec)[lit. ***], IR (KBr) 3414, 2945, 2868, 1760, 167, 1449, 1384, 1524, 1213, 1068, 1025, 967, 495cm^{-1}; ^{1}H NMR (CDC13/DMSOd6=1:1) d 5.64 (S, 2H, (OH)2) 3.94 (S, 1H, 19H), 3.81 (M, 1H, 3-H), 1.001, 0.98, 0.98, 0.89, 0.89, 0.87, 0.78 (all S, 7x3H, 23-, 24-, 25-, 26-, 27-, 29-, 30-Me), 1.05-1.95 (complex CH-, CH_2-, 23H); ^{13}C NMR ($CDCl_3$/DMSOd6) d 177.852, 84,195, 82.504, 53.984, 49.510, 44.897, 44.431, 38.995, 38.405, 38.405, 37.275, 37.181, 35.556, 34.608, 32.065, 30.928, 30.243, 27.38, 26.637, 26.345, 24.851, 24.057, 23.758, 22.381, 19.408, 16.712, 15.174, 14.817, 14.059, 12.296; 31P NMR (D_3PO_4 85% in D_2O) d-0.719.

Example 22

Allobetulin-3-hydroxy-3-aminomethyl

3-aminomethyl-3-hydroxy-28,19-β-epoxy-oleanan

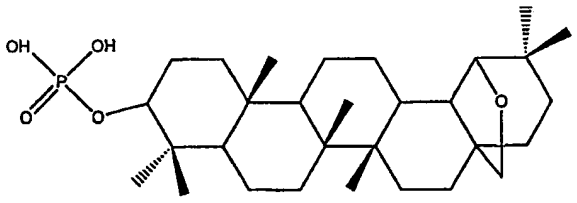


In 25 mL round bottom flask boil the mixture of allobetulon (0.86 g, 1.955 mmol), ZnI_2 (20 mg, 0.063 mmol) and tret-butyldimethylsilylcyanide (0.420 g, 3.78 mmol) in 15 mL of Toluene for 24 hours. Add the above mentioned mixture to a suspension of $LiAlH_4$ (0.37 g, 10 mmol) in 30 mL of THF drop wise and boil for 2 hours. Next, add 0.5 mL of concentrated KOH, dilute with 30 mL of THF and filter with diatomaceous earth. Dry over sodium sulfate and bubble HCl gas through the THF solution and filter the white precipitate (0.98 g). Dissolve the crystals in 50 mL of chloroform and wash with 1% $NaHCO_3$ until neutral reaction of universal paper indicator. Separate organic part and dry over sodium sulfate. Evaporation of solvent gives 0.89 g (96% yield) of white crystalline compound mp. 222.0-224.3°C, IR (KBr) 3414, 2939, 2868, 1617, 1461, 1384, 1036 cm^{-1}; ^1H NMR ($CDCl_3$) d 3.67 (D, 1H, 28H, J=7.5 Hz), 3.521 (S, 1H, 19H), 3.437 (D, 1H, 28H, J=7.5 Hz), 2.95 (D, 1H, 31H, J=13.2Hz), 2.757 (D, 1H, 31H, J=13.2 Hz), 2.523 (S, 3H, OH+NH_2), 0.972, 0.926, 0.911, 0.904, 0.894, 0.824, 0.798 (all S, 7x3H, 23-, 24-, 25-, 26-, 27-, 29-, 30-Me), 1.01-1.79 (complex CH-, CH_2-, 24H); ^{13}C NMR ($CDCl_3$) d 88.13, 75.174, 71.428, 62.517, 53.554, 51.703, 47.018, 43.265, 41.669, 40.911, 40.882, 40.882, 37.683, 37.596, 36.933, 36.459, 34.309, 32.903, 30.265, 29.048, 27.416, 26.643, 26.454, 24.771, 24.166, 21.171, 19.947, 18.905, 17.076, 15.961, 13.811.

Example 22

Allobetulin-3-phosphate

28,19-β-epoxy-oleanan-3-phosphate



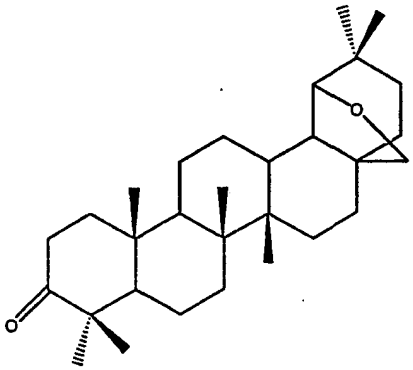
In 100 mL round bottom flask boil a solution of Allobetulin-3-phosphodichloride in 50 mL of dioxane and 1 mL of water for 18 hours. Dilute with cold water (50 mL) and filter white precipitate. Wash on filter with water (3x30 mL). Dry in oven (temperature not higher than 110°C) to give 3.12 g of white crystalline compound mp. 167.0-168.1°C (dec), IR (KBr) 3469,

2947, 2868, 1775, 1467, 1388, 1221, 1169, 1022, 884, 585, 505, 481 cm^{-1}; ^1H NMR; ^{31}P NMR (D_3PO_4 85% in D_2O) d-0.684.

Example 23

Allobetulon

oleanan-3-one-28,19-β-ether



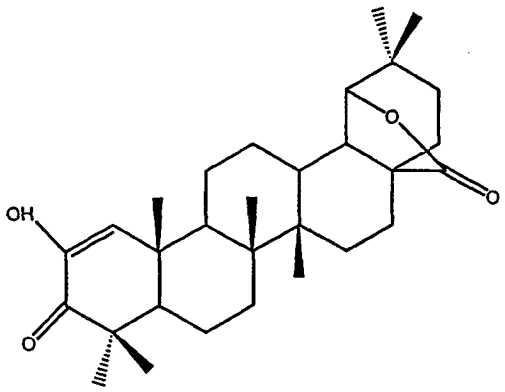
In 100-mL round bottom two neck flask place 11 mmol (1.397 g) $(COCl)_2$ in 25 ml of dry CH_2Cl_2 at -50-60°C (i-Pr alcohol - dry ice bath) and with efficient stirring add 22 mmol (1.76 g) of dry DMSO in 25 ml of dry CH_2Cl_2 in drop wise in 3-5 minutes. Stir the mixture for additional 5 minutes and then add crystals of allobetulin (10 mmol, 4.43 g). Stand solution for 30-45 minutes and after adding with 25 mmol (2.53 g) of triethylamine; remove cold bath and let temperature to increase up to 10°C. Pour the mixture in 100 ml of cracked ice, extract with CH_2Cl_2 (3x20 ml) and wash combined organic extracts with water (5x10 ml), 5% HCl (2x10 ml), and H_2O (2x10 ml). After drying over sodium sulfate solvent evaporation gives 4.4 g of crude compound, which after column chromatography (hexane:ether=80:20) gives 4.31 g of white crystals mp. 228.8-233.1°C [lit. 230-235°C], IR (KBr) 2949, 2859, 1774, 1702, 1457, 1382, 1167, 1034 cm^{-1}; ^1H NMR ($CDCl_3$) d 3.74 (D, J=10.3 Hz, 1H, 28-H), 3.48 (S, 1-H, 19-H), 3.39 (D, J=10.3 Hz, 1H, 28-H), 2.37 (M, 2H, 2-H,H), 1.85 (M, 1H, 19-H), 0.72, 0.81, 0.815, 0.91, 0.92, 0.99 (all S, 7x3H, 27-, 23-, 24-, 25-, 26-, 29-, 30-Me), 1.01-1.54 (complex CH-, CH_2, 25H); ^{13}C NMR ($CDCl_3$) d 218.08, 88.01, 71.39, 55.08, 50.55, 47.43, 46.92, 41.60, 40.91, 40.68, 39.97,

37.11, 36.88, 36.43, 34.41, 34.23, 33.33, 32.86, 29.00, 26.92, 26.60, 26.60, 26.40, 24.73, 21.68, 21.16, 19.79, 16.52, 15.68, 13.63; MS (EI) 440, 422, 411, 369, 355, 281, 220, 207, 205, 191, 177, 163, 149, 135, 121.

Example 24

Allobetulonlactone-1-ene-2-ol

2-hydroxy-olean-1,2-ene-3-one-28,19-β-lactone



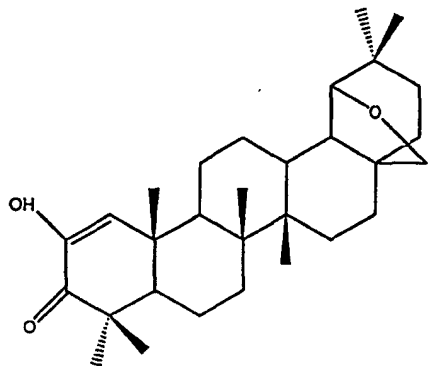
To a solution of Allobetulonlactone (1.0 g) in dry benzene - tert-butyl alcohol (1:1, 40 ml) was added a solution of potassium tert-butoxide (0.56 g) in tert-butyl (20 ml) and oxygen was bubbled into the stirred mixture for 3 hours. The mixture was acidified with 2.0 ml of glacial acetic acid and extracted with CH_2Cl_2. After washing with water (2x15 ml), 5% aqueous $NaHCO_3$ (2x30 ml) and water (30 ml), the extract was dried over Na_2SO_4 and evaporated to give crystals (m=0.983 g, 98%), which after chromatography on silica gel (hexane: ether=40:60) yields a white crystalline compound mp. 238.8-243.6°C, IR (KBr) 3451, 2944, 2864, 1764, 1663, 1642, 1450, 1405, 1384, 1234, 1055, 967 cm^{-1}; ^1H NMR ($CDCl_3$) d 6.47 (S, 1H, 2-H), 6.07-5.85 (1H, OH), 3.96 (S, 1H, 19H), 1.207, 1.153, 1.109, 1.037, 0.98, 0.974, 0.877 (all S, 7x3H, 23-, 24-, 25-, 26-, 27-, 20-, 30-Me), 1.05-1.91 (complex CH-, CH_2, 22H); ^{13}C NMR ($CDCl_3$) d 201.36, 180.025 144.217, 128.966, 86.192, 54.501, 46.879, 46.631, 46.376, 44.292, 41.654, 40.525, 38.936, 36.393, 33.836, 33.632, 32.568, 32.174, 29.034, 28.006, 27.365, 26.571, 25.784, 24.232, 21.841, 21.397, 20.923, 18.868, 16.282, 13.768, MS (EI) 468, 454, 441, 425,

407, 369, 340, 313, 303, 269, 259, 234, 215, 207, 189, 176, 165, 153, 151, 135, 128, 124, 108, 95, 78, 69, 55, 43.

Example 25

Allobetulon-1-ene-2-ol.

2-hydroxy-28,19-β-epoxy-olean-1(2)-ene-3-one

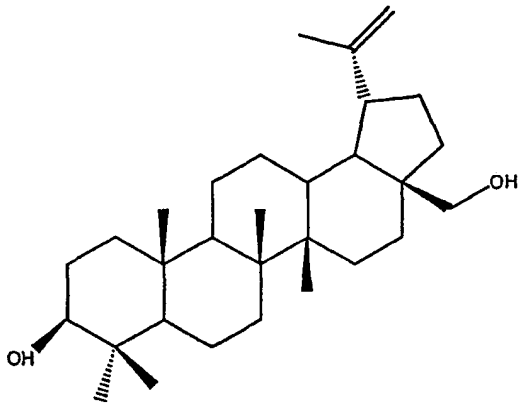


To a solution of allobetulon (1.8 g) in dry benzene - tert-butyl alcohol (1:1, 40 ml) was added a solution of potassium tert-butoxide (1.2 g) in tert-butyl (20 ml) and oxygen was bubbled into the stirred mixture for 1.5 hours. The mixture was acidified with 2.5 ml of glacial acetic acid and extracted with CH_2Cl_2. After washing with water (2x15 ml), 5% aqueous $NaHCO_3$ (2x30 ml) and water (30 ml), the extract was dried over Na_2SO_4 and evaporated to give crystals, which after chromatography on silica gel (hexane: ether=85:15) 1402, 1234, 1058, 1035 cm^{-1}; ^1H NMR ($CDCl_3$) d 6.46 (S, 1H, 1-H), 5.9 (S, 1H, 2-OH), 3.75 (D, 1H, 28H), 3.52 (S, 1H, 19-H), 3.52 (S, 1H, 28H), 0.78, 0.91, 0.99, 1.01, 1.09, 1.13, 1.19 (all S, 7x3, 23-, 24-, 25-, 26-, 27-, 29-, 30-Me), 1.05-1.78 (complex CH-, CH_2, 25H); ^{13}C NMR ($CDCl_3$) d 201.43, 144.202, 129.29, 88.16, 71.523, 54.49, 46.99, 44.3, 41.75, 41.312, 38.97, 36.98, 36.56, 34.53, 33.83, 32.97, 29.1, 27.41, 26.6, 26.52, 24.86, 21.89, 21.51, 20.87, 18.96, 16.5, 13.64; MS (EI) 454 383, 327, 281, 245, 215, 207, 191, 177, 151, 137, 136, 123, 109, 95, 81, 69, 55.

Example 26

Betulin

lup-20(29)-ene-3,28-diol



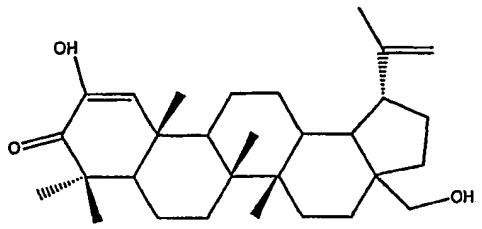
Isolation of Betulin.

Betulin was isolated from paper birch (B. papyrifera) bark. Shredded, dry bark (500 g) has been extracted with chloroform on a Soxhlet apparatus for 10 hours. The extract was evaporated and then was left ovemight at 5-7°C. Crystals were filtered and washed with hexane and then dried in oven to give 94.5 g of crude Betulin. Double crystallization from chloroform and then mixture of chloroform-isopropyl alcohol(4:1) gives 64-68 g of pure Betulin mp. 258-259°C [lit. mp 256-261°C]. IR (KBr) 3378, 2942, 2868, 1645, 1453, 1374, 1106, 1031, 880 cm^{-1}; ^1H NMR ($CDCl_3$) d 4.68 (S, 1H, 29-H), 4.58 (S, 1H, 29-H), 3.8 (D, J=10.3 Hz, 1H, 28-H, 3.34 (D, J=10.3 Hz, 1H, 28-H), 3.18 (DD, 1H, 3-H), 2.38 (M, 1H, 19-H), 1.68 (S, 3H, 30-Me), 0.76, 0.82, 0.97, 0.98, 1.02 (all S, 5x3H, 27-, 23-, 24-, 25-, 26-Me), 1.01-2.4 (complex CH-, CH_2, 25 H,); ^{13}C NMR ($CDCl_3$) d 151.249, 110.464, 79.736, 61.278, 56.017, 51.12, 49.48, 48.533, 48.534, 43.454, 41.647, 39.614, 39.432, 38.033, 37.894, 34.958, 34.725, 30.469, 29.901, 28.742, 28.123, 27.773, 25.929, 21.572, 19.845, 19.051, 16.879, 16.726, 16.136, 15.516; MS (EI) 442, 424, 411, 398, 393, 381, 288, 234, 207, 203, 189, 175, 161, 147, 135, 121, 107.

Example 27

Betulon-1-ene-2-ol.

lup-1(2),20(29)-diene-2,28-diol-3-one

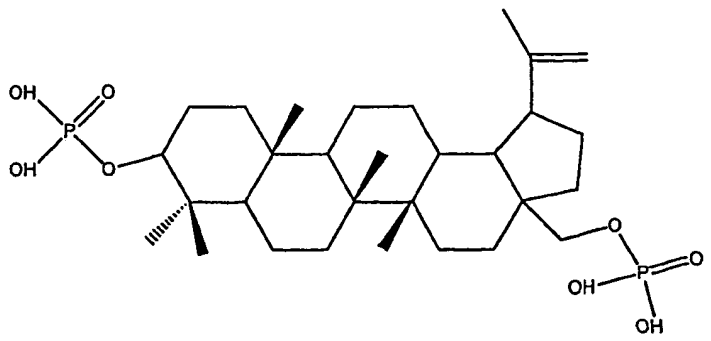


To a solution of betulin-28-acetate (1.0 g) in dry benzene - tert-butyl alcohol (1:1, 40 ml) was added a solution of potassium tert-butoxide (1.05 g) in tert-butanol (20 ml). Oxygen was bubbled into the stirred mixture for 1.5 hours. The mixture was acidified with 2.2 ml of glacial acetic acid and extracted with CH_2C1_2. After washing with water (2x15 ml), 5% aqueous $NaHCO_3$ (2x30 ml) and water (30 ml), the extract was dried over Na_2SO_4 and evaporated to give crystals, which after chromatography on silica gel (hexane:ether=80:20) yielded a white crystalline compound mp. 167-170 (dec) °C, IR (KBr) 3446, 2944, 2870, 1717, 1669, 1647, 1457, 1406, 1237, 1032, 882 cm^{-1}; ^1H NMR ($CDCl_3$) d 6.43(S, 1H, 2-H), 6.12-5.81 (OH), 4.69 (S, 1H, 29H), 4.60 (S, 1H, 29H), 3.79 (DD, 1H, 28-H, J=10.7 Hz), 3.35 (DD, 1H, 28-H, J=10.7 Hz), 2.4 (M, 1H, 19-H), 1.69 (S, 3H, 30-Me), 1.203, 1.124, 1.105, 1.09, 0.976 (all S, 5x3H, 23-, 24-, 25-, 26-, 27-Me), 1.05-2.01 (complex CH-, CH_2 22H); ^{13}C NMR ($CDCl_3$) d 201.513, 150.491, 144.188, 129.228, 110.209, 60.768, 54.217, 48.883, 48.045, 48.045, 45.844, 44.278, 43.309, 42.019, 38.893, 37.654, 34 244, 34.149, 29.974, 29.398, 27.409, 27.226, 25.332, 21.907, 21.353, 20.457, 19.364, 19.021, 16.755 114.941; MS (EI) 454, 438, 424, 381, 325, 302, 271, 229, 215, 189, 177, 161, 135, 121, 95, 81, 55.

Example 28

Betulin-3,28-diphosphaate

Lup-20(29)-ene-3,28-diphosphate

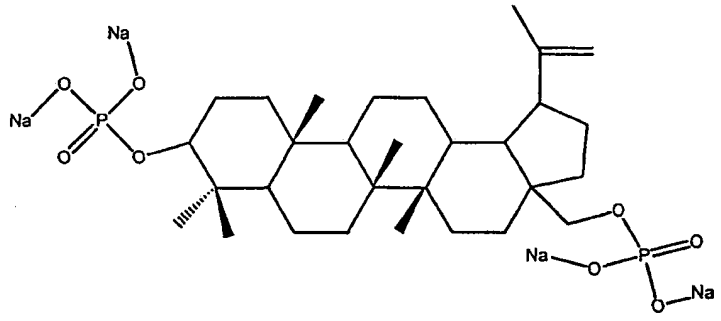


In 100 mL round bottom flask boil a solution of betulin-3,28-diphosphodichloride in 50 mL of dioxane and 1 mL of water for 18 hours. Dilute with cold water (50 mL) and filtrate white precipitate. Wash on filter with water (3x30 mL). Dry in oven (temperature not higher than 110°C).

Example 29

Betulin-3,28-diphosphate sodium salt

Lup-20(29)-ene-3,28-sodiumdiphosphate

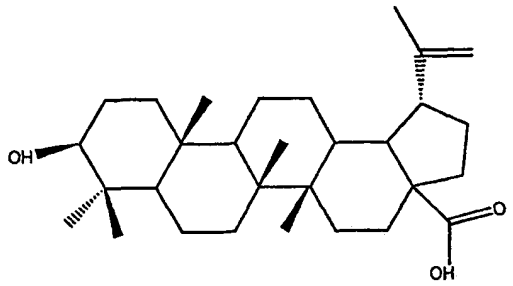


In 100 mL round bottom flask to a suspension of 1 g (1.66 mmol) of betulin-3,28-diphosphate in 40 mL of water a solution of 0.6 g of sodium bicarbonate in 40 ml of water was added dropwise to maintain pH <=7. Water was evaporated under reduced pressure and white precipitate was dried in vacuum.

Example 30

Betulinic acid

3-hydroxy-lup-20(29)-ene-28-oic acid



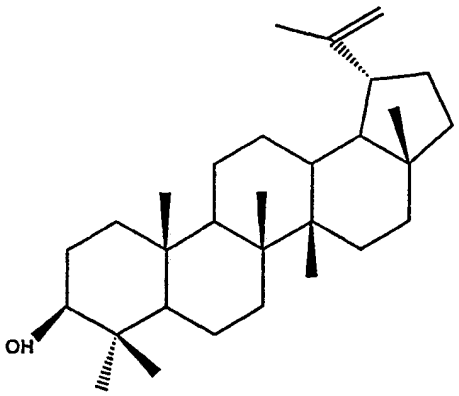
Betulinic aldehyde (1.5 g) was dissolved in 45 ml of ethyl acetate and then was placed in a 100 ml heatable column. 0.6 ml of distilled water and 23 mg of ABIN was added to the solution. Oxygen has been bubbled through the mixture at 50-60°C for 6 hours with periodic addition of ABIN (5 mg per hour). Evaporation of solvent and following crystallization from MeOH gives 1.42 g of white crystals mp. 288-291°C [lit. 291-292], IR (KBr) 3449, 2941, 2869, 1686, 1639, 1451, 1376, 1235, 1186, 1043, 886 cm^{-1}; ^1H NMR ($CDCl_3$), d 4.79 (S, 1H, 29 H), 4.65 (S, 1 H, 29H), 3.22 (DD, 1H. 3-H), 3.02 (T, 1 H, 19H), 1.66 (S, 3 H, 30-Me), 0.79, 0.83, 0.88, 1.0, 1.0 (all S, 5x3H, 23-, 24-, 25-, 26-, 27-Me), 1.05-2.24 (complex CH-, CH_2, 25H); ^{13}C NMR ($CDCl_3$) d 180.403, 150.542, 109.86, 79.146, 56.433, 55.471, 50.64, 49.401, 47.025, 42.573, 40.824, 39.01, 38.842, 38.529, 37.348, 37.174, 34.456, 32.291, 30.688, 29.85, 28.138, 27.54, 25.631, 20.982, 19.518, 18.417, 16.282, 16.173, 15.495. 14.847; MS (EI) (after sililation) 518, 510, 487, 483, 471, 456, 428, 413, 393, 377, 353, 320, 306, 292, 257, 203, 189, 175, 148, 135, 129, 73.

Example 31

Lupeol,

monoglynol B, β-viscol, fagarasterol

lup-20(29)-ene-3β-ol

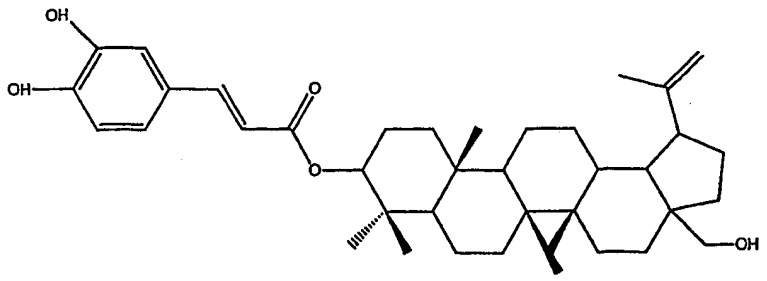


Combined parts after Betulin crystallization and solvent evaporation were separated on silica gel (eluent hex: ether=10:1). After 150 ml solvent delay 20 fractions were collected. Fractions 1-7 contain mixture of lower terpenes, fractions 8-13 contained Lupeol mp 182.7-187.3 °C, IR (KBr) 3380, 2920, 1450, 1405, 1025, 940 cm^{-1}; ^1H NMR ($CDCl_3$) d 4.69 (S, 1H, 29-H), 4.55 (S, 1H, 29-H), 3.18 (DD, 1H, 3-H), 2.35 (M, 1H, 19-H), 1.67 (S, 3H, 30-Me), 0.74, 0.76, 0.80, 0.92, 0.94, 1.01 (all S, 6x3H, 27-, 23-, 24-, 25-, 26-, 28- Me), 1.01-2.4 (complex CH-, CH_2, 25 H,); ^{13}C NMR ($CDCl_3$) d 151.32, 109.67, 79.32, 55.63, 50.77, 48.63, 48.33, 43.34, 43.17, 41.16, 40.34, 39.20, 39.04, 38.38, 37.50, 35.92, 34.61, 30.18, 28.33, 27.77, 26.09, 25.47, 21.26, 19.65, 18.65, 18.35, 16.46, 16.31, 15.72, 14.89; MS (EI) 426, 411, 393, 381, 369, 315, 281, 257, 218, 207, 189, 175, 161, 147, 135, 121, 107.

Example 32

Betulin-28-caffeate

Lup-20(29)-ene-28-ol-3-caffeate



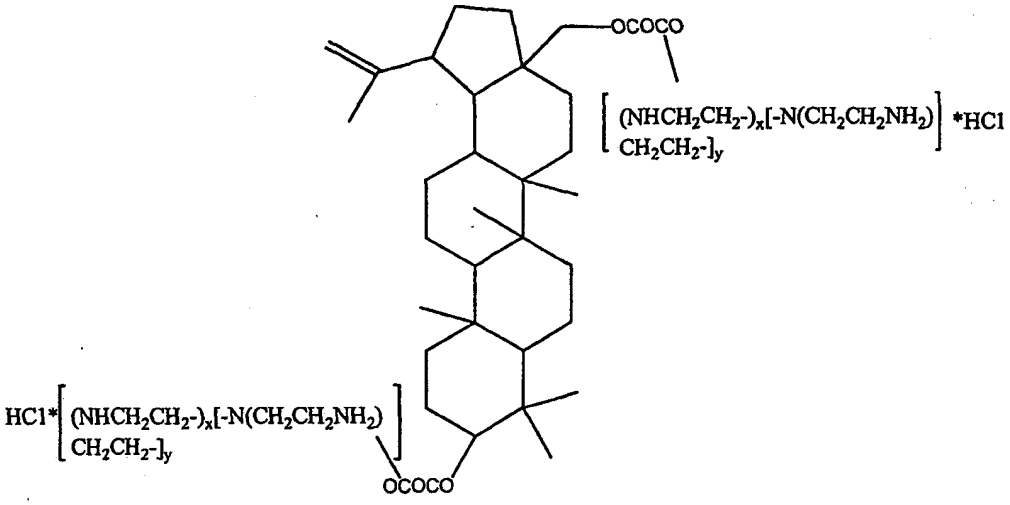
In a one liter round bottom one neck flask equipped with condenser a crude extract of outer birch bark (100 g) was dissolved in 500 ml of tetrahydrofuran. 10 g of aluminum triisopropoxide was added. The mixture was boiled for 1 hour, was allowed to cool to 45°C. This formed a precipitate, which was filtered and washed with tetrahydrofuran (5x40 ml) and dried on filter. Residual powder (34.2 g) was washed with 10% AcOH, dried on filter and extracted with 1% AcOH in isopropyl alcohol (5x50 ml). Combined extracts were concentrated in vacuum to 50 ml volume and diluted with water (200 ml) and filtered, and dried in vacuum at 40°C. The resulting 22.7 g of material was treated with a solution of diazomethane in diethyl ether and solvent was evaporated after no more nitrogen evolved. The remaining material was subjected for chromatography on silica gel (hexanes:ether=4:1) and 30 fractions were collected after 100 ml solvent delay and analyzed by TLC. Fractions 7, 8, 9 were combined and solvent was evaporated to give 4.78 g of lite-yellow crystals m.p. 191.1, 198.3°C, IR (KBr) 3426, 2945, 2871, 1708, 1678, 1630, 1604, 1514, 1447, 1376, 1273, 1181, 1109, 1012, 977 cm^{-1}; ^1H NMR ($CDCl_3$), 7.602 (1H, DJ=15.9, C3'H from caffeate); 7.1 (1H, D, J=7.8, C2'-H from caffeate); 7.06 (1H, D, J=2); 6.86 (1H, DD, J=7.8, C5'H); 6.314 (1H, D, J=15.9); 4.68 (1H, S, 29-H); 4.62 (1H, M, C3H); 4.59 (1H, S, 29H); 3.82 (1H, D, J=11.5, 28H); 3.35 (1H, D, J=11.5, 28H), 1.69 (3H, S, 30-Me), 1.036, 0.991, 0.927, 0.899, 0.882 (5x3H, S, 23-, 24-, 25-, 26-, 27-Me); 1.05-2.24 (complex CH-, CH_2); ^{13}C NMR ($CDCl_3$) 167.44, 151.29, 150.8, 149.47, 144.54, 127.82, 122.92, 116.83, 111.27, 110.06, 109.78, 81.141, 60.86, 56.28, 55.73, 50.62, 49.06, 48.11, 43.04, 41.264, 38.739, 38.39, 37.61, 37.42, 34.87, 34.30, 30.03, 29.47, 28.33, 27.35, 25.48, 24.165, 21.18, 19.39, 18.53, 17.03, 16.53, 16.31, 15.06.

Example 33

General Procedure for preparation of Betulin-3,28-dioxalate-polyethylenimine amids (samples 49-51, 100-106):

In 500 ml round bottom flask to a solution of polyethylenimine (MW_{av} 600) (a mmol) in 100 ml of dichloromethane add a solution of Betulin-3,28-dioxalylchloride (b mmol) in 300 ml of dichloromethane drop wise while stirring at 21-23°C. The reaction mixture was then stirred for 15 minutes and dichloromethane was evaporated under reduced pressure at 40°C. Residue (oily amorphous material) was dried in vacuum.

49. Betulin-3,28-dioxalylchloride:polyethylenimine (MW_{av} 600) ratio a:b=1:1;
50. Betulin-3,28-dioxalylchloride:polyethylenimine (MW_{av} 600) ratio a:b=1:3;
51. Betulin-3,28-dioxalylchloride:polyethylenimine (MW_{av} 600) ratio a:b=5:1;
100. Betulin-3,28-dioxalylchloride:polyethylenimine (MW_{av} 600) ratio a:b=1:5;
101. Betulin-3,28-dioxalylchloride:polyethylenimine (MW_{av} 600) ratio a:b=3:1;
102. Betulin-3,28-dioxalylchloride:polyethylenimine (MW_{av} 600) ratio a:b=1:10;
103. Betulin-3,28-dioxalylchloride:polyethylenimine (MW_{av} 600) ratio a:b=1:1;
104. Betulin-3,28-dioxalylchloride:polyethylenimine (MW_{av} 600) ratio a:b=1:2;
105. Betulin-3,28-dioxalylchloride:polyethylenimine (MW_{av} 600) ratio a:b=2:1;
106. Betulin-3,28-dioxalylchloride:polyethylenimine (MW_{av} 600) ratio a:b=1:4.



Example 34

In this example the anti-fungal properties of betulin and its derivatives were determined by the agar dilution method.

Agar dilution method. Sabouraud Dextrose Agar (Difco Laboratories, Michigan) was prepared according to the manufacturer's instructions. Five ml was dispensed in a 100 x 25 mm tube and autoclaved. To each tube containing 5.0 ml of liquid agar at 45 °C, 0.5, 0.25, 0.12, or 0.063 ml of a DMSO solution of the compound was added to give the final indicated concentrations in Table 2. The agar was then solidified in slants. Fungal cultures were inoculated. The slants were incubated at 25-28 °C for 10-12 days, and the growth of the fungus was recorded every second day.

Results

The results of the assays of growth inhibition by the agar dilution method with various strains of fungi are shown in Table 2. The compounds exhibiting the best antifungal or anti-yeast activity by the agar dilution method were the following:

Betulin, betulin-28-maleate, allobetulin-3-glutarate, betulin-28-phthalate, allobetulin-3-succinate against *Microsporum canis*.

Betulin, allobetulin, betulin-28-succinate, betulin-3,28-disuccinate, betulin-3-maleate, allobetulin-3-glutarate, against *Microsporum audouinii*.

Allobetulin-3-glutarate and betulin-3,28-diphthalate against *Trichophyton tonsurans*.

Betulin-3,28-didiglycolate against *Trichophyton mentagrophytes*.

Betulin-3,28-diphthalate against *Epidermophyton floccosum*.

Table 2. Antifungal activities of betulin and derivatives against human pathogenic fungi.

Test Antifungal Compounds	Concentration µg/ml in DMSO	*Microsporum canis*	*Microsporum audouinni*	*Microsporum gypseum*	*Trichophyton tonsuran*	*Trichophyton rubrum*	*Trichophyton mentagrophyte*	*Epidermophyton floccosum*	*Pityrosporum ovale*
	100	–	–	–	–	–	–	–	+/–
Betulin	50	+/–	–	++	++	+	+/–	–	++
1 mg/ml	25	+	+/–	++	++	++	+	+	+++
	12.5	++	+/–	+++	+++	++	++	+	+++
	75	–	–	–	–	–	–	–	–
Allobetulin	38	++	–	++	++	+	+	+	++
0.75 mg/ml	19	++	–	++	++	++	+	+	+++
	9	+++	+/–	+++	+++	++	++	++	+++
	1000	–	–	–	–	–	–	–	++
Betulin 28-succinate	500	+	–	+	+	+	+	+	+++
10 mg/ml	250	+	+/–	+	+	+	+	+	+++
	125	+	+	++	++	+	++	++	+++
	1000	–	–	–	–	–	–	–	+/–
Betulin 3-maleate	500	+/–	–	++	+	+	+/–	–	++
10 mg/ml	250	+/–	+/–	++	++	++	+	+	+++
	125	+	+/–	+++	++	++	++	++	+++

Test Antifungal Compounds	Concentration µg/ml in DMSO	*Microsporum canis*	*Microsporum audouinni*	*Microsporum gypseum*	*Trichophyton tonsuran*	*Trichophyton rubrum*	*Trichophyton mentagrophyte*	*Epidermophyton floccosum*	*Pityrosporum ovale*
Allobetulin 3-glutarate 1 mg/ml	100	-	-	-	-	-	-	-	-
	50	-	-	++	-	+	+	+	+
	25	+/-	+/-	++	+/-	++	+	+	++
	12.5	+	+	+++	+	++	++	++	++
Betulin 3,28-didiglycolate 10 mg/ml	1000	-	-	-	-	-	-	-	-/+
	500	+	-	++	+	+	+/-	-	++
	250	++	++	+++	+	+	+	+	++
	125	++	++	+++	++	++	+	++	++
Betulin 28-phthalate 1 mg/ml	100	-	-	-	-	-	-	-	-
	50	-	-	++	-	+	+	+	+
	25	+	+	++	+	+	++	++	++
	12.5	++	++	+++	++	++	+++	+++	++
Betulin 3,28-diphathalate 10 mg/ml	1000	-	-	-	-	-	-	-	+
	500	-	-	-	+/-	+	-	+/-	++
	250	+	+	+	++	++	+	++	++
	125	++	++	++	+++	++	++	++	++

Test Antifungal Compounds	Concentration µg/ml in DMSO	*Microsporum canis*	*Microsporum audouinni*	*Microsporum gypseum*	*Trichophyton tonsuran*	*Trichophyton rubrum*	*Trichophyton mentagrophyte*	*Epidermophyton floccosum*	*Pityrosporum ovale*
Allobetulin 3-succinate 5 mg/ml	500	-	-	-	-	-	-	-	+
	250	-	-	+	+	-	+/-	+	++
	125	++	++	++	++	++	+	++	++
	62.5	++	++	+++	++	++	++	++	++
Betulin 3,28-disuccinate 10 mg/ml	1000	-	-	-	-	-	-	-	+
	500	+	-	+	+	+	+	+	++
	250	+	-	+	+	+	+	+	++
	125	++	+	++	++	++	++	++	++
Griseofulvin 10 mg/ml	1000	-	-	-	-	-	-	-	-
	500	-	-	-	-	-	-	-	+
	250	+/-	-	+/-	+/-	+/-	+	+	++
	125	+/-	-	+/-	+/-	+/-	++	++	++
Nystatin 10 mg/ml	1000	-	-	-	-	-	-	-	-
	500	-	-	-	-	+/-	-	-	-
	250	+/-	-	+/-	+/-	+	+	-	+/-
	125	+	-	+	+	+	+	+/-	+

Test Antifungal Compounds	Concentration µg/ml in DMSO	*Microsporum canis*	*Microsporum audouinni*	*Microsporum gypseum*	*Trichophyton tonsuran*	*Trichophyton rubrum*	*Trichophyton mentagrophyte*	*Epidermophyton floccosum*	*Pityrosporum ovale*
DMSO Control	0.5 ml	-	-	-	-	-	-	-	-
	0.25 ml	+	-	++	++	+	+	+	++
	0.12 ml	+	+	++	++	+	+	+	+++
	0.062 ml	++	+	+++	+++	++	++	++	+++
Fungi Control		+++	+++	+++	+++	+++	+++	+++	+++

Fungal growth was measured at the 12th day after inoculation

+++ = Maximum Fungal Growth

++ = Moderate Fungal Growth

+ = Minimum Fungal Growth

+/- = Very little Fungal Growth

- = No Fungal Growth

Example 35

In this example, the antifungal properties of betulin and its derivatives were determined by the direct addition method and the disk diffusion method.

Direct addition method. Sabouraud dextrose agar was prepared according to the manufacturer's instructions and 5.0 ml was dispensed in each 100 x 25 mm tube. The tubes were autoclaved. To each tube containing 5.0 ml of liquid agar at 45 °C, 20 mg of solid test compound was added, to give a final concentration of 4 mg/ml. The agar was solidified in slants. The fungal cultures were then innoculated. The slants were incubated at 25-28 °C for 10-12 days, and the growth of the fungus was recorded every second day. The results in Table 2 indicate growth at the 12th day of inoculation.

Disk diffusion method. Sabouraud dextrose agar was prepared according to the manufacturer's directions, autoclaved, and solidified in sterile petri dishes. Yeast cultures were spread over the surface with a cotton swab. Filter paper disks of 10 mm diameter were each impregnated with one of the test chemicals and then placed on the plate with sterile forceps. The disks were impregnated with 10 µl of a DMSO solution of the test compound at concentrations varying from 1-10 mg/ml. Zones of inhibition were measured after 24 hours.

Results

The results of the assays of growth inhibition by the direct addition method with various strains of fungi are shown in Table 3. The compounds exhibiting the best anti-fungal or anti-yeast activity by the direct addition method were the following:

Betulin-3,28-diglycine, betulin-3,28-disuccinate, and betulin-28-maleate against *Microsporum canis*.

Betulin, allobetulin-3-L-valine, betulin-3,28-dimaleate, and betulin-28-succinate against *Microsporum audouinii*.

Betulin and betulin-3,28-di-L-valine against *Trichophyton rubrum*.

Using the disk diffusion method, no compounds were found to inhibit growth of *Pityrosporum ovale* (data not shown). However, by direct addition assays, several compounds were found to inhibit growth of *P. ovale*. The results of direct addition assays against *P. ovale* are shown in Table 4.

Against *Pityrosporum ovale*, allobetulin, allobetulin-3-L-valine, betulin-28-glutarate, and

betulin-3,28-diglutarate inhibited the growth by the direct addition method at 4 mg/ml. However, minimum inhibitory concentrations were not determined. This is comparable to the result with Nystatin, the standard drug against *P. ovale* infection, which also inhibits growth at 4 mg/ml.

Table 3. Antifungal activities of betulin and derivatives against human pathogenic fungi.

Test Antifungal Compounds	Concentration mg/mL of agar	*Microsporum canis*	*Epidermophyton floccosum*	*Microsporum audouinni*	*Trichophyton rubrum*	*Pityrosporum ovale*	*Microsporum gypseum*	*Trichophyton tonsuran*	*Trichophyton mentagrophytes*
Betulin	4 mg	+	-	-	-	-	++	++	++
Allobetulin	4 mg	++	-	+	+	-	NP	NP	NP
Betulin-3,28-diglycine	4 mg	+/-	-	+	+	-	NP	NP	NP
Betulin-3,28-di-L-valine	4 mg	+	-	+	+/-	-	NP	NP	NP
Allobetulin-3-L-valine	4 mg	+	-	-	+	-	NP	NP	NP
Allobetulin-3-glycine	4 mg	+	-	+	++	-	NP	NP	NP
Betuline-3,28-dimaleate	4 mg	+	-	-	+	-	NP	NP	NP
Betulin-28-succinate	4 mg	+	-	-	+	-	NP	NP	NP
Betulin-3,28-disuccinate	4 mg	-	-	+	+	-	NP	NP	NP
Allobetulin-3-succinate	4 mg	+	-	+	+	-	NP	NP	NP
Allobetulin-3-glutarate	4 mg	+	-	+	+	-	NP	NP	NP

Test Antifungal Compounds	Concentration mg/mL of agar	*Microsporum canis*	*Epidermophyton floccosum*	*Microsporum audouinni*	*Trichophyton rubrum*	*Pityrosporum ovale*	*Microsporum gypseum*	*Trichophyton tonsuran*	*Trichophyton mentagrophytes*
Betulin 28-glutarate	4 mg	+	-	+	+	-	NP	NP	NP
Betulin 3, 28-diglutarate	4 mg	+	-	+	+	-	NP	NP	NP
Betulin 28-maleate	4 mg	-	-	++	++	-	+++	++	++
Lupeol	4 mg	+	-	+	+	-	NP	NP	NP
Lupeol-3-succinate	4 mg	+	-	+	+	-	NP	NP	NP
Griseofulvin	4 mg	-	-	-	-	-	NP	NP	NP
Nystatin	4 mg	-	-	-	+/-	-	NP	NP	NP
Control	-	++	-	++	+	-	+++	+++	+++
Betulin α CD	0.1 mg	+	-	+	+	-	NP	NP	NP
Betulin β CD	0.1 mg	+	-	-	+	-	NP	NP	NP
Control	-	+	-	+	+	-	NP	NP	NP

Fungal growth at the 12th day after inoculation

+++ = Maximum Fungal Growth

++ = Moderate Fungal Growth

+ = Minimum Fungal Growth

+/- = Very Little Fungal Growth

- = No Fungal Growth

NP = Assay not performed

Table 4. Anti *Pityrosporum ovale* activity of different compounds by direct addition into the Pityrosporum agar.

	Test Compound	Concentration of compound in the agar	*Pityrosporum ovale* growth
1.	Allobetulin	4 mg/ml	+/-
2.	Betulin-3,28-diglycine	4 mg/ml	+
3.	Betulin-3,28-di-L-valine	4 mg/ml	+/-
4.	Allobetulin-3-L-valine	4 mg/ml	+
5.	Allobetulin-3-glycine	4 mg/ml	+
6.	Betulin-3,28-dimaleate	4 mg/ml	+
7.	Betulin-28-succinate	4 mg/ml	+
8.	Betulin-3,28-disuccinate	4 mg/ml	+
9.	Allobetulin-3-succinate	4 mg/ml	+
10.	Allobetulin-3-glutarate	4 mg/ml	+
11.	Betulin-28-glutarate	4 mg/ml	+/-
12.	Betulin-3,28-diglutarate	4 mg/ml	+/-
13.	Lupeol	4 mg/ml	+
14.	Lupeol-3-succinate	4 mg/ml	+
	Control Drugs		
15.	Nystatin	4 mg/ml	+/-
16.	Griseofulvin	4 mg/ml	+
	Growth Control		
17.	*P. ovale* Growth Control	No Compound	++

Pityrosporum ovale growth measured 18 hours after inoculation

+++ = Maximum Growth

++ = Moderate Growth

+ = Minimum Growth

+/- = Very Little Growth

- = No Growth

Example 36

In this example, derivatives of lupeol were tested for their activity in inhibiting the growth of *Trichophyton mentagraphytes* in liquid culture.

Direct addition to liquid culture method. Sabouraud dextrose broth was prepared according to the manufacturer's instructions, and 7.0 ml was dispensed into 100 x 25 mm tubes and autoclaved. To each tube containing 7.0 ml of liquid broth, the test compounds dissolved in DMSO were added to final concentrations of 25, 50, and 100 µg/ml. The tubes were then inoculated with 150 µl of a fungus suspension and incubated at 25-28 °C for 10-12 days. Growth was measured every second day by measuring optical density at 600 nm against a blank containing sterile broth.

Results.

The optical density of the cultures of *Trichophyton mentagrophytes* after 12 days of growth in broth with various concentrations of the test compounds is shown in FIG. 1. The full names of the compounds listed in the figure are as follows. "Maleate" refers to lupeol-3-maleate. "Diketone" refers to lupenon-1,2-ene-2-ol. "Dimethylsuccinate" refers to lupeol-3-(3',3'-dimethyl)succinate. "Amine" refers to lupeol-3-amine.

Lupeol and all of its derivatives that were tested inhibited the growth of the fungus. The degree of inhibition with 100 µg/ml of the test compounds was comparable to the extent of inhibition with 50 or 100 µg/ml of Nystatin or Lamisil, two standard anti-fungal compounds.

Example 37

This example summarizes the results of various other assays of the anti-fungal activity of betulin derivatives. The results are shown in Table 5. Table 5 summarizes results using different assay methods--direct addition, agar dilution, and direct addition to liquid culture, as disclosed in

the previous three Examples. In some cases, only one type of assay was done with a compound. In other cases, the compound was tested by multiple assays.

Table 5 shows that the following compounds were active.

Allobetulin-3-succinate and Betulin-3,28-dioxalate-3-polyethyleneimine against *Candida albicans.*

Betulin-3,28-dioxalate-3,28-polyethyleneimine against *Candida guilliermoundii.*

Betulin-3,28-dioxalate-3,28-polyethyleneimine against *Blastomyces dermaidis.*

Betulin-3,28-dioxalate-3,28-polyethyleneimine against *Crytococcus neoformans.*

Allobetulin-3-succinate, allobetulin-3-glutarate, betulin, betulin-3,28-di(3',3'-dimethyl)glutarate, betulin-28-glutarate, betulin-28-phthalate, betulin-28-diglycolate, betulin-3,28-diphthalate, and betulin-3,28-dioxalate-3,28-polyethyleneimine against *Microsporum canis.*

Allobetulin-3-succinate, allobetulin-3-glutarate, betulin-3-maleate, betulin, betulin-3,28-di(3',3'-dimethyl)glutarate, betulin-28-glutarate, betulin-28-phthalate, betulin-28-diglycolate, betulin-3,28-diphthalate, betulin-28-succinate, betulin-3,28-disuccinate, and betulin-3,28-dioxalate-3,28-polyethyleneimine against *Microsporum audouinii.*

Betulin-3,28-di(3',3'-dimethyl)glutarate, betulin-28-glutarate, betulin-28-diglycolate, betulin-3,28-diphthalate, and betulin-3,28-dioxalate-3,28-polyethyleneimine against *Microsporum gypseum.*

Betulin-3,28-di(3',3'-dimethyl)glutarate, betulin-28-glutarate, betulin-28-phthalate, betulin-28-diglycolate, betulin-3,28-diphthalate, and betulin-3,28-dioxalate-3,28-polyethyleneimine against *Trichophyton tonsurans.*

Allobetulin-3-succinate, betulin-3,28-di(3',3'-dimethyl)glutarate, betulin-28-glutarate, betulin-28-phthalate, betulin-28-diglycolate, and betulin-3,28-dioxalate-3,28-polyethyleneimine against *Trichophyton rubrum.*

Allobetulin-3-succinate, betulin, betulin-3,28-di(3',3'-dimethyl)glutarate, betulin-28-glutarate, betulin-28-diglycolate, betulin-3,28-diphthalate, and betulin-3,28-dioxalate-3,28-polyethyleneimine against *Trichophyton mentagrophytes.*

Betulin-3,28-di(3',3'-dimethyl)glutarate, betulin-28-glutarate, betulin-28-diglycolate, betulin-3,28-diphthalate, and betulin-3,28-dioxalate-3,28-polyethyleneimine against *Epidermophyton floccosum.*

Table 5. Activity of compounds against human pathogenic fungi and yeasts.

S.No. Compound	*Candida albicans*	*Candida guilliermoundii*	*P. ovale*	*Blastomyces dermatidis*	*Crytococcus neoformans*	*Microsporum canis*	*Microsporum audouinii*	*Microsporum gypseum*	*Trichophyton tonsurans*	*Trichophyton rubrum*	*Trichophyton mentagrophytes*	*Epidermophyton floccosum*
Allobetulin	x	x	x			x	o	x	x	x	x	x
Allobetulin-3-succinate	o	x	x	x	x	x	x	x	x	x	x	x
Allobetulin-3-glycine			x			x	x	x	x	x	x	x
Allobetulin-3-L-alanine ester			x									
Allobetulin L-valine ester						x	x	x	x	x	x	x
Allobetulin-3-succinate			x			o	o	x	x	o	o	x
Allobetulin-3-glutarate	x	x	x			o	o	x	x	x	x	x
Allobetulin glutarate			x			x	x	x	x	x	x	x
Allobetulin-3-phthalate	x	x	x			x	x	x	x	x	x	x
Allobetulin-3-glutarate			x			x	x	x	x	x	x	x
Allobetulin-3-phosphate						x	x	x	x	x	x	x
Allosbetulon-1-ene-2-diglycolate	x	x										
3-Allobetulon-1-ene-2-diglycolate	x	x										
Betulin	x	x	x			o	o	x	x	x	o	x

S.No. Compound	*Candida albicans*	*Candida guilliermoundii*	*P. ovale*	*Blastomyces dermatidis*	*Crytococcus neoformans*	*Microsporum canis*	*Microsporum audouinii*	*Microsporum gypseum*	*Trichophyton tonsurans*	*Trichophyton rubrum*	*Trichophyton mentagrophytes*	*Epidermophyton floccosum*
Betulin-3,28-diglycine		x				x	x	x	x	x	x	x
Betulin-3-maleate		x				x	o	x	x	x	x	x
Betulin-3,28-dioxalate-PEI*2HCl						x	x	x	x	x	x	x
Betulin-3,28-dioxalate-PEI HCl mole ratio=6:1	o	x		x	x							
Betulin-3,28-diphosphate						x	x	x	x	x	x	x
Betulin-3-caffeate	x	x										
Betulin-3,28-(3',3'-dimethyl) glutarate						o	o	o	o	o	o	o
Betulin-28-diglycolate						x	x	x	x	x	x	x
Betulin-28-glutarate			x			o	o	o	o	o	o	o
Betulin-28-maleate						x	x	x	x	x	x	x
Betulin-28-phthalate			x			o	o	x	o	x	x	x
Betulin-3,28-di-(3',3'-dimethyl)glutarate						x	x	x	x	x	x	x
Betulin-3,28-didiglycolate			x			x	x	x	x	x	x	x
Betulin-3,28-di(thiodiglycolate)			x			x	x	x	x	x	x	x

S.No. Compound	*Candida albicans*	*Candida guilliermoundii*	*P. ovale*	*Blastomyces dermatidis*	*Crytococcus neoformans*	*Microsporum canis*	*Microsporum audouinii*	*Microsporum gypseum*	*Trichophyton tonsurans*	*Trichophyton rubrum*	*Trichophyton mentagrophytes*	*Epidermophyton floccosum*
Betulin-3,28-diglutarate			x			x	x	x	x	x	x	x
Betulin-3,28-dimaleate			x			x	x	x	x	x	x	x
Betulin-28-diglycolate						o	o	o	o	o	o	o
Betulin-3,28-diphthalate			x			o	o	o	o	x	o	o
Betulin-3,28-di-L-valine ester			x			x	x	x	x	x	x	x
Betulin-28-succinate			x			x	o	x	x	x	x	x
Betulin-3,28-disuccinate			x			x	o	x	x	x	x	x
Betulinic acid			x			x	x	x	x	x	x	x
Lupeol	x	x	x			x	x	x	x	x	x	x
Lupeol-3-glutarate	x	x										
Lupeol-3-succinate	x	x	x			x	x	x	x	x	x	x
Lupeol-3-thiodiglycolate	x	x		x	x	x	x	x	x	x	x	x
Lupeol-3-phthalate	x	x		x	x							
Oleanolic acid	x	x										
Betulin-3,28-dioxalate-(polyethyleneimine) m=6.0g mole ratio (1/5)	o	o		o	o	o	o	o	o	o	o	o

S.No. Compound	*Candida albicans*	*Candida guilliermoundii*	*P. ovale*	*Blastomyces dermatidis*	*Crytococcus neoformans*	*Microsporum canis*	*Microsporum audouinii*	*Microsporum gypseum*	*Trichophyton tonsurans*	*Trichophyton rubrum*	*Trichophyton mentagrophytes*	*Epidermophyton floccosum*
Betulin-3,28-dioxalate-(polyethyleneimine) m=1.5g mole ratio (3/1)	x	x		x	x							
Betulin-3,28-dioxalate-PEI mole ratio (1/1)	x	o		x	x							
Betulin-3,28-dioxalate-PEI (1/2)	o	o		o	x							
Betulin-3,28-dioxalate-PEI (2/1)	x	o		o	x							
Betulin3,28-dioxalate-PEI (1/4)	o	o		o	o							
Polyethyleneimine	o	o		o	o							
Polyethyleneimine, Av.Mw-25,000				o	x							
Polyethyleneimine low mol.wt Mw-2000				x	x							
Polyethyleneimine 50% wt soln Av.Mw 1200				o	x							
Polyethyleneimine Av.Mw 75,000 50% wt. solu				x	x							

Compounds active in any of the above four examples against at least one species of fungus, including yeast, are the following:

Allobetulin

Allobetulin-3-succinate

Allobetulin-3-glutarate

Allobetulin-3-L-valine

Betulin

Betulin-3-maleate

Betulin-28-diglycolate

Betulin-28-glutarate

Betulin-28-maleate

Betulin-28-phthalate

Betulin-28-succinate

Betulin-3,28-diglycine

Betulin-3,28-didiglycolate

Betulin-3,28-dimaleate

Betulin-3,28-dioxalate-3-polyethyleneimine

Betulin-3,28-di(3',3'-dimethyl)glutarate

Betulin-3,28-dioxalate-3,28-polyethyleneimine

Betulin-3,28-diphthalate

Betulin-3,28-disuccinate

Betulin-3,28-di-L-valine

Lupeol

Lupeol-3-amine

Lupeol-3-(3',3'-dimethyl)succinate

Lupeol-3-maleate

Lupenone

Lupenon-1,2-ene-2-ol.

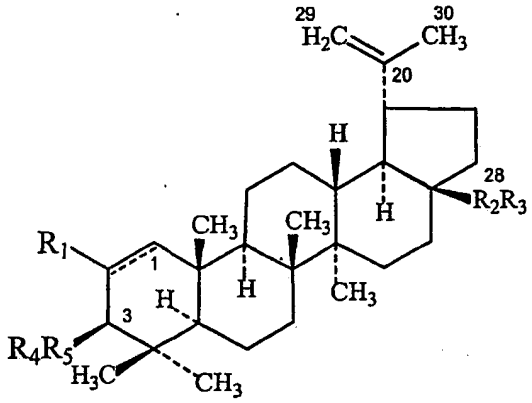
All publications, patents, and patent documents are incorporated by reference herein, as

though individually incorporated by reference. The invention has been described with reference to various specific and preferred embodiments and techniques. However, it should be understood that many variations and modifications may be made while remaining within the spirit and scope of the invention.

Claims

What is claimed is:

1. The use of a compound of formula (I):



(I)

wherein

R_1 is hydrogen or hydroxy;

R_2 is a direct bond, carbonyl, oxy, thio, carbonyl oxy, oxy carbonyl, $(C_6\text{-}C_{10})$aryl, or $(C_1\text{-}C_6)$alkyl;

R_3 is hydrogen, hydroxy, $(C_1\text{-}C_6)$alkyl, $O{=}P(OH)_2$, $O{=}P(OH)_2OP(O)(OH)$-, $(C_1\text{-}C_5)$alkanoyl, $Si(R)_3$ wherein each R is H, phenyl or $(C_1\text{-}C_6)$alkyl, $C(O)N(R)_2$, benzyl, benzoyl, tetrahydropyran-2-yl, 1-$[(C_1\text{-}C_4)$alkoxy$](C_1\text{-}C_4)$alkyl, or a glycoside;

R_4 is hydrogen, hydroxy, $(C_1\text{-}C_6)$alkyl, $O{=}P(OH)_2$, $O{=}P(OH)_2OP(O)(OH)$-, $(C_1\text{-}C_5)$alkanoyl, $Si(R)_3$ wherein each R is H, phenyl or $(C_1\text{-}C_6)$alkyl, $C(O)N(R)_2$, benzyl, benzoyl, tetrahydropyran-2-yl, 1-$[(C_1\text{-}C_4)$alkoxy$](C_1\text{-}C_4)$alkyl, or a glycoside; or R_4 and R_5 together are oxo; and

R_5 is direct bond, carbonyl, oxy, thio, carbonyl oxy, oxy carbonyl, $(C_6\text{-}C_{10})$aryl, or $(C_1\text{-}C_6)$alkyl; or R_4 and R_5 together are oxo;

wherein any alkyl can optionally be substituted with one or more halo, hydroxy, $(C_6\text{-}C_{10})$aryl, nitro, cyano, $(C_1\text{-}C_6)$alkoxy, trifluoromethyl, polyethyleneimine, poly(ethylene glycol), oxo, NR_7R_8, wherein R_7 and R_8 are each independently hydrogen, $(C_1\text{-}C_6)$alkyl or

polyethyleneimine; or C(=O)OR_9, wherein R_9 is hydrogen, (C_1-C_6)alkyl, or polyethyleneimine;

each of the bonds represented by --- is independently absent or is present;

wherein any alkyl is optionally interrupted on carbon with one or more oxy, thio, sulfinyl, sulfonyl, polyethyleneimine, or poly(ethylene glycol);

wherein any alkyl is optionally partially unsaturated;

wherein any aryl can optionally be substituted with one or more halo, hydroxy, nitro, cyano, (C_1-C_6)alkoxy, trifluoromethyl, polyethyleneimine, poly(ethylene glycol), oxo, NR_7R_8, wherein R_7 and R_8 are each independently hydrogen, (C_1-C_6)alkyl or polyethyleneimine; or C(=O)OR_9, wherein R_9 is hydrogen, (C_1-C_6)alkyl, or polyethyleneimine;

or a pharmaceutically acceptable salt thereof;

for the manufacture of a medicament for treating a mammal afflicted with a fungal or yeast infection.

2. The use of a compound of claim 1 wherein the bond between carbons 1 and 2 is a single bond.

3. The use of a compound of claim 1 wherein the bond between carbons 1 and 2 is a double bond.

4. The use of a compound of claim 1 wherein R_1 is hydrogen.

5. The use of a compound of claim 1 wherein R_1 is hydroxy.

6. The use of a compound of claim 1 wherein R_2 is a direct bond.

7. The use of a compound of claim 1 wherein R_3 is (C_1-C_6)alkyl; wherein

any alkyl can optionally be substituted with one or more oxo, carboxy, amino, -OP(=O)$(OH)_2$, or phenyl;

any alkyl is optionally interrupted on carbon with one or more oxy or thio;

any alkyl is optionally partially unsaturated; and

any aryl can optionally be substituted with one or more hydroxy or carboxy.

8. The use of a compound of claim 7 wherein R_3 is hydroxymethyl, (carboxymethoxy)acetoxymethyl, 4-carboxybutanoyloxymethyl, 3-carboxypropenoyloxymethyl, 2-carboxybenzoyloxymethyl, 3-carboxypropanoyloxymethyl, aminoacetoxymethyl, carboxycarbonyloxymethyl, 2-amino-3-methyl-butanoyloxymethyl, 4-carboxy-(3,3-dimethyl)butanoyloxymethyl, or $-CH_2OC(=O)C(=O)-(-NHCH_2CH_2)_x-[-N(CH_2CH_2NH_2)CH_2CH_2]_y$.

9. The use of a compound of claim 1 wherein R_4 is hydrogen or (C_1-C_6)alkyl; wherein

any alkyl can optionally be substituted with one or more oxo, carboxy, amino, $-OP(=O)(OH)_2$, or phenyl;

any alkyl is optionally interrupted on carbon with one or more oxy or thio;

any alkyl is optionally partially unsaturated; and

any aryl can optionally be substituted with one or more hydroxy or carboxy.

10. The use of a compound of claim 9 wherein R_4 is hydrogen, hydroxymethyl, (carboxymethoxy)acetyl, 4-carboxybutanoyl, 3-carboxypropenoyl, 2-carboxybenzoyl, 3-carboxypropanoyl, aminoacetyl, carboxycarbonyl, 2-amino-3-methyl-butanoyl, 4-carboxy-(3,3-dimethyl)butanoyl, 3-carboxy-3-methylbutanoyl or $-C(=O)C(=O)-(-NHCH_2CH_2)_x-[-N(CH_2CH_2NH_2)CH_2CH_2]_y$.

10. The use of a compound of claim 1 wherein R_5 is oxy.

11. The use of a compound of claim 1 wherein R_4 and R_5 together are oxo.

12. The use of a compound of claim 1 wherein

R_1 is hydrogen or hydroxy;

R_2 is a direct bond;

R_3 is (C_1-C_6)alkyl;

R_4 is hydrogen or $(C_1\text{-}C_6)$alkyl; and

R_5 is oxy or R_4 and R_5 together are oxo;

wherein

any alkyl can optionally be substituted with one or more oxo, carboxy, amino, $-OP(=O)(OH)_2$, or phenyl;

any alkyl is optionally interrupted on carbon with one or more oxy or thio;

any alkyl is optionally partially unsaturated; and

any aryl can optionally be substituted with one or more hydroxy or carboxy.

13. The use of a compound of claim 1 wherein

R_1 is hydrogen or hydroxy;

R_2 is a direct bond;

R_3 is hydroxymethyl, (carboxymethoxy)acetoxymethyl, 4-carboxybutanoyloxymethyl, 3-carboxypropenoyloxymethyl, 2-carboxybenzoyloxymethyl, 3-carboxypropanoyloxymethyl, aminoacetoxymethyl, carboxycarbonyloxymethyl, 2-amino-3-methyl-butanoyloxymethyl, 4-carboxy-(3,3-dimethyl)butanoyloxymethyl, or $-CH_2OC(=O)C(=O)\text{-}(\text{-}NHCH_2CH_2)_x\text{-}[\text{-}N(CH_2CH_2NH_2)CH_2CH_2]_y$;

R_4 is hydrogen, hydroxymethyl, (carboxymethoxy)acetyl, 4-carboxybutanoyl, 3-carboxypropenoyl, 2-carboxybenzoyl, 3-carboxypropanoyl, aminoacetyl, carboxycarbonyl, 2-amino-3-methyl-butanoyl, 4-carboxy-(3,3-dimethyl)butanoyl, 3-carboxy-3-methylbutanoyl or $-C(=O)C(=O)\text{-}(\text{-}NHCH_2CH_2)_x\text{-}[\text{-}N(CH_2CH_2NH_2)CH_2CH_2]_y$.; and

R_5 is oxy or R_4 and R_5 together are oxo.

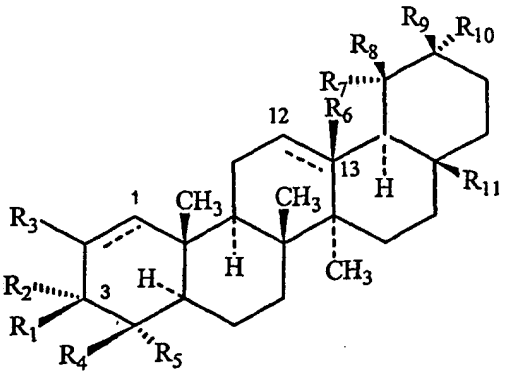
14. The use of a compound of claim 1 wherein the triterpene is betulin; betulin-3,28-diglycine; betulin-28-glycerol oxalate; betulin-28-glycine; betulin-28-oxalate; betulin arabinose galactan; betulin-3,28-diglycolate; betulin-3-maleate; betulin-3,28-di-(L-glutamic acid γ-benzylester) ester; betulin-3,28-di-L-alanine; betulin-3,28-di-L-proline ester; betulin-3,28-dioxalate; betulin-1-ene-2-ol; betulin-3,28-diphenylalanine; betulin-3,28- dioxalate-polyethylene amine; betulin-3,28-diphosphate; betulin-3-caffeate; betulin-3,28-(3',3'-dimethyl)glutarate; betulin-28-diglycolate; betulin-28-glutarate; betulin-28-maleate; betulin-28-phthalate; betulin-

3,28-di(3',3'-dimethyl) glutarate; betulin-3,28-didiglycolate; betulin-3,28-dithiodiglycolate; betulin-3,28-diglutarate; betulin-3,28-dimaleate; betulin-3,28-diglycolate; betulin-3,28-diphthalate; betulin-3,28-di-L-valine ester; betulin-28-succinate; betulin-3,28-disuccinate; betulin-3,28-di-(polyethylene glycol)-COOH (Mw=1448); betulin-3,28-di-(polyethylene glycol)-COOH (Mw=906); betulin-3,28-di-(polyethylene glycol)-COOH (Mw=906); betulinic acid; betulon-1-ene-2-ol; betulin-3,28-(dipoly(ethylene glycol)bis (carboxymethylester); hederin hydrate; lupeol; lupeol-3-glutarate; lupeol-3-succinate; lupeol-3-thiodiglycolate; lupeol-3-phthalate; oleanolic acid; ursolic acid; or uvaol.

15. The use of a compound of claim 1 wherein the triterpene is betulin; betulin-3,28-diglycine; betulin-28-glycerol oxalate; betulin-28-glycine; betulin oxalate; betulin arabinose galactan; betulin-3,28-diglycolate; betulin-3-maleate; betulin di-(L-glutamic acid γ-benzylester) ester; betulin 3,28-di-L-alanine; betulin3,28-di-L-proline; betulin-3,28-dioxalate; betulin-1-ene-2-ol; betulin-3,28-diphenylalanine ester; betulin-3,28-dioxalate-(polyethylene amine); betulin-3-caffeate; betulin-3,28-(3',3'-dimethyl)glutarate; betulin-28-diglycolate; betulin-28-glutarate; betulin-28-phthalate; betulin-3,28-diglycolate; betulin-3,28-diphthalate; betulin-3,28-phosphate; betulin-28-succinate; betulin-3,28-disuccinate; betulin-3,28-di-(polyethylene glycol)-COOH (Mw=1448); betulin-3,28-di-(polyethylene glycol)-COOH (Mw=906 crude); betulin-3,28-di-(polyethylene glycol)-COOH (Mw=906); betulon-1-ene-2-ol; betulin-3,28-(dipoly(ethylene glycol)bis(carboxymethylester); hederin hydrate; lupeol-3-succinate; lupeol-3-phthalate; lupeol-3-glutarate; oleanolic acid; ursolic acid; or uvaol.

16. The use of a compound of claim 1 wherein the triterpene is betulin; betulin-3-maleate; betulin-28-diglycolate; betulin-28-glutarate; betulin-28-maleate; betulin-28-phthalate; betulin-28-succinate; betulin-3,28-diglycine; betulin-3,28-didiglycolate; betulin-3,28-dimaleate; betulin-3,28-dioxalate-3-polyethyleneimine; betulin-3,28-di(3',3'-dimethyl)glutarate; betulin-3,28-dioxalate-3,28-polyethyleneimine; betulin-3,28-diphthalate; betulin-3,28-disuccinate; betulin-3,28-di-L-valine; lupeol; lupeol-3-amine; lupeol-3-(3',3'-dimethyl)succinate; lupeol-3-maleate; lupenone; or lupenon-1,2-ene-2-ol.

17. The use of a compound of formula (II):



(II)

wherein

one of R_1 and R_2 is -O-Y and the other is hydrogen or $(C_1$-$C_6)$alkyl optionally substituted by hydroxy, $(C_1$-$C_6)$alkoxy, halo, halo$(C_1$-$C_6)$alkoxy or NR_jR_k wherein R_j and R_k are independently H, $(C_1$-$C_6)$alkyl or $(C_1$-$C_6)$alkonyl; or R_1 and R_2 together are oxo (=O);

R_3 is hydrogen, halo, carboxy, mercapto, $(C_1$-$C_6)$alkyl, $(C_3$-$C_8)$cycloalkyl, or -O-Y;

R_4 and R_5 are each independently hydrogen, $(C_1$-$C_6)$alkyl, or hydroxy$(C_1$-$C_6)$alkyl;

R_6 is hydrogen or is absent when the adjacent --- is a bond;

R_7 is hydrogen or $(C_1$-$C_6)$alkyl;

R_8 is hydrogen, $(C_1$-$C_6)$alkyl, or hydroxy$(C_1$-$C_6)$alkyl and R_{11} is hydrogen, $(C_1$-$C_6)$alkyl, carboxy, or hydroxy$(C_1$-$C_6)$alkyl; or R_8 and R_{11} together are -O-C(=X)-;

R_9 and R_{10}, are each independently hydrogen or $(C_1$-$C_6)$alkyl;

each of the bonds represented by --- is independently absent or is present;

X is two hydrogens, oxo (=O) or thioxo (=S);

each Y is independently H, aryl, $P(O)(Cl)_2$, $(C_3$-$C_8)$cycloalkyl, adamantyl, $-SO_2R_a$ $O=P(R_b)_2$, $O=P(R_c)_2OP(O)(R_d)$-, $Si(R_e)_3$, tetrahydropyran-2-yl, an amino acid, a peptide, a glycoside, or a 1 to 10 membered branched or unbranched carbon chain optionally comprising 1, 2, or 3 heteroatoms selected from non-peroxide oxy, thio, and $-N(R_f)$-; wherein said chain may optionally be substituted on carbon with 1, 2, 3, or 4 oxo (=O), hydroxy, carboxy, halo,

mercapto, nitro, -N(R_g)(R_h), (C_3-C_8)cycloalkyl, (C_3-C_8)cycloalkyloxy, aryl, aryloxy, adamantyl, adamantyloxy, hydroxyamino, trifluoroacetylamino, a glycoside, an amino acid, or a peptide; and wherein said chain may optionally be saturated or unsaturated (e.g. containing one, two, three or more, double or triple bonds);

R_a is (C_1-C_6)alkyl or aryl;

R_b, R_c, and R_d are each independently hydroxy, (C_1-C_6)alkoxy, hydroxy(C_2-C_6)alkoxy, adamantyloxy, adamantyl(C_1-C_6)alkoxy, norbornyloxy, 1,1-di(hydroxymethyl)-2-hydroxyethoxy, carboxy(C_1-C_6)alkoxy, 2,3-epoxypropyloxy, benzyloxy, (C_3-C_8)cycloalkyloxy, NR_xR_y, or aryloxy;

R_e is H, aryl or (C_1-C_6)alkyl;

R_f is hydrogen, (C_1-C_6)alkyl, (C_1-C_6)alkanoyl, phenyl or benzyl;

R_g and R_h are each independently selected from the group consisting of hydrogen, (C_1-C_6)alkyl, hydroxy(C_1-C_6)alkyl, adamantyl, adamantyl(C_1-C_6)alkyl, amino(C_1-C_6)alkyl, aminosulfonyl, (C_1-C_6)alkanoyl, aryl and benzyl; or R_b and R_c together with the nitrogen to which they are attached form a pyrrolidino, piperidino, or morpholino radical; and

R_x and R_y are each independently hydrogen, (C_1-C_6)alkyl, (C_1-C_6)alkanoyl, aryl or benzyl;

wherein each aryl of Y, R_a-R_d , R_g-R_h , R_x, and R_y may optionally be substituted by 1, 2, or 3 aminosulfonyl, carboxy, NR_iR_j, (C_1-C_6)alkyl, (C_1-C_6)alkoxy, hydroxy, halo, nitro, cyano, mercapto, carboxy, hydroxy(C_1-C_6)alkyl, halo(C_1-C_6)alkyl, trifluoromethoxy, (C_1-C_6)alkanoyl, (C_1-C_6)alkoxycarbonyl, (C_1-C_6)alkylthio, or (C_1-C_6)alkanoyloxy; wherein R_i and R_j are each independently hydrogen, (C_1-C_6)alkyl, (C_1-C_6)alkanoyl, phenyl, or benzyl;

wherein any alkyl can optionally be substituted with one or more polyethyleneimine or poly(ethylene glycol); and wherein any alkyl can optionally be interrupted with one or more polyethyleneimine or poly(ethylene glycol);

or a pharmaceutically acceptable salt thereof;

for the manufacture of a medicament for treating a mammal afflicted with a fungal or yeast infection.

18. The use of a compound of claim 17 wherein the bond between carbons 1 and 2 is a single

bond.

19. The use of a compound of claim 17 wherein R_1 is -O-Y and Y is hydrogen, an amino acid, or (C_1-C_6)alkyl; wherein

any alkyl can be optionally substituted with one or more oxo, hydroxy, amino, phenyl, or carboxy

any alky can be optionally interrupted with one or more oxy or thio;

any phenyl can be optionally substituted with one or more hydroxy or carboxy.

20. The use of a compound of claim 17 wherein R_1 is -O-Y and Y is hydrogen, 3-carboxypropanoyl, 4-carboxybutanoyl, or 2-amino-2-methylbutanoyl.

21. The use of a compound of claim 17 wherein R_2 is hydrogen.

22. The use of a compound of claim 17 wherein R_3 is hydrogen.

23. The use of a compound of claim 17 wherein R_4 is methyl.

24. The use of a compound of claim 17 wherein R_5 is methyl.

25. The use of a compound of claim 17 wherein R_6 is hydrogen and the bond between carbons 12 and 13 is a single bond.

26. The use of a compound of claim 17 wherein R_7 is hydrogen.

27. The use of a compound of claim 17 wherein R_8 and R_{11} together are -O-CH_2-.

28. The use of a compound of claim 17 wherein R_9 is methyl.

29. The use of a compound of claim 17 wherein R_{10} is methyl.

30. The use of a compound of claim 17 wherein

R_1 is -O-Y and Y is hydrogen, an amino acid, or (C_1-C_6)alkyl; wherein

the alkyl of Y can be optionally substituted with one or more oxo, hydroxy, amino, carboxy, or phenyl optionally substituted with one or more hydroxy or carboxy;

and can be optionally interrupted with one or more oxy or thio;

R_2 is hydrogen;

R_3 is hydrogen and the bond between carbons 1 and 2 is a single bond;

R_4 and R_5 are each methyl;

R_6 is hydrogen and the bond between carbons 12 and 13 is a single bond;

R_7 is hydrogen

R_8 and R_{11} together are -O-CH_2-; and

R_9 and R_{10} are each methyl.

31. The use of a compound of claim 17 wherein the triterpene is 3-β-acetoxy-19αH-19,28 lactone oleanan; allobetulin; allobetulin-3-succinate; allobetulin-3-glycine; allobetulin lactone; allobetulin lactone-3-acetate; allobetulin lactone-3-phosphate; allobetulin-3-L-alanine; allobetulin-3-L-valine; allobetulin-3-L-proline ester; allobetulin-3-succinate; allobetulin-3-diglycolate; allobetulin-3-phthalate; allobetulin-3-methylenamine; allobetulin-3-ethanolamine; allobetulin-3-glycolate; allobetulin-3-glutarate; allobetulin-28-glutarate; allobetulin-3-methylamine HCl; allobetulin-3-phosphate; allobetulin-3-(polyethylene glycol)-COOH (Mw=674); allobetulon; allobetulon lactone 1-ene-2-ol; allobetulon lactone-1-en-2-succinate; allobetulon-1-ene-2-ol; allobetulon-1-ene-2-diglycolate; 3-allobetulon-1-ene-2-succinate; allobetulin-3-(poly(ethylene glycol)bis (carboxymethyl ester); or 3-allobetulon-1-ene-2-diglycolate.

32. The use of a compound of claim 17 wherein the triterpene is 3-β-acetoxy-19αH-19,28 lactone oleanan; allobetulin; allobetulin-3-succinate; allobetulin lactone; allobetulin lactone-3-acetate; allobetulin lactone-3-phosphate; allobetulin-3-L-valine; allobetulin-3-L-proline; allobetulin-3-succinate; allobetulin-3-diglycolate; allobetulin-3-methylenamine; allobetulin-3-ethanolamine; allobetulin-3-glycolate; allobetulin-3- glutarate; allobetulin-3-glutarate;

allobetulin-3-(polyethylene glycol)-COOH (Mw=674); allobetulon; allobetulon lactone 1-ene-2-ol; allobetulon lactone-1-en-2-succinate; allobetulon-1-ene-2-ol; allobetulon-1-ene-2-diglycolate; 3-allobetulon-1-ene-2-succinate; or allobetulin-3-(poly(ethylene glycol)bis(carboxymethyl ester).

33. The use of a compound of claim 17 wherein the triterpene is allobetulin, allobetulin-3-glutarate, allobetulin-3-succinate, or allobetulin-3-L-valine.

34. The use of a compound of claim 1 or 17 wherein the mammal is a human.

35. The use of a compound of claim 1 or 17 wherein the fungal infection is caused by a dermatophytic fungus.

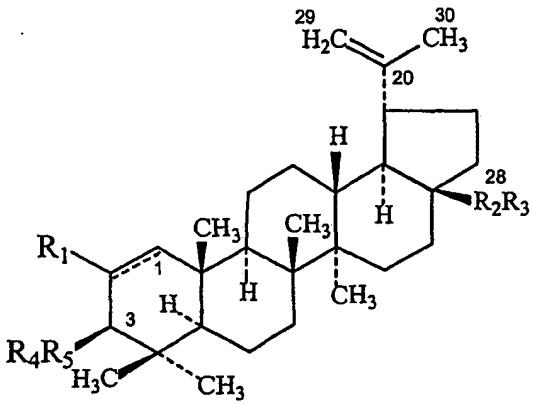
36. The use of a compound of claim 1 or 17 wherein the dermatophytic fungus is *Microsporum canis*, *Microsporum gypseum*, *Microsporum audouinii*, *Trichophyton tonsurans*, *Trichophyton mentagrophytes*, *Epidermophyton floccosum*, *Trichophyton rubrum*, or *Pityrosporum ovale*.

37. The use of a compound of claim 1 or 17 wherein the fungal infection is caused by *Candida albicans* or *Candida guilliermoundi*.

38. The use of a compound of claim 1 or 17 wherein the fungal infection is caused by *Blastomyces dermatidis* or *Cryptococcus neoformans*.

39. The use of a compound of claim 1 or 17 wherein the yeast infection is caused by *Pityrosporum ovale*.

40. A method of inhibiting or killing a fungus or yeast comprising contacting the fungus or yeast with an effective anti-fungal or anti-yeast amount of a triterpene of formula (I):



(I)

wherein

R_1 is hydrogen or hydroxy;

R_2 is a direct bond, carbonyl, oxy, thio, carbonyl oxy, oxy carbonyl, $(C_6$-$C_{10})$aryl, or $(C_1$-$C_6)$alkyl;

R_3 is hydrogen, hydroxy, $(C_1$-$C_6)$alkyl, $O=P(OH)_2$, $O=P(OH)_2$, $O=P(OH)_2OP(O)(OH)$-, $(C_1$-$C_5)$alkanoyl, $Si(R)_3$ wherein each R is H, phenyl or $(C_1$-$C_6)$alkyl, $C(O)N(R)_2$, benzyl, benzoyl, tetrahydropyran-2-yl, 1-[$(C_1$-$C_4)$alkoxy]$(C_1$-$C_4)$alkyl, or a glycoside;

R_4 is hydrogen, hydroxy, $(C_1$-$C_6)$alkyl, $O=P(OH)_2$, $O=P(OH)_2$, $O=P(OH)_2OP(O)(OH)$-, $(C_1$-$C_5)$alkanoyl, $Si(R)_3$ wherein each R is H, phenyl or $(C_1$-$C_6)$alkyl, $C(O)N(R)_2$, benzyl, benzoyl, tetrahydropyran-2-yl, 1-[$(C_1$-$C_4)$alkoxy]$(C_1$-$C_4)$alkyl, or a glycoside; or R_4 and R_5 together are oxo; and

R_5 is direct bond, carbonyl, oxy, thio, carbonyl oxy, oxy carbonyl, $(C_6$-$C_{10})$aryl, or $(C_1$-$C_6)$alkyl; or R_4 and R_5 together are oxo;

wherein any alkyl can optionally be substituted with one or more halo, hydroxy, $(C_6$-$C_{10})$aryl, nitro, cyano, $(C_1$-$C_6)$alkoxy, trifluoromethyl, polyethyleneimine, poly(ethylene glycol), oxo, NR_7R_8, wherein R_7 and R_8 are each independently hydrogen, $(C_1$-$C_6)$alkyl or polyethyleneimine; or $C(=O)OR_9$, wherein R_9 is hydrogen, $(C_1$-$C_6)$alkyl, or polyethyleneimine;

each of the bonds represented by --- is independently absent or is present;

wherein any alkyl is optionally interrupted on carbon with one or more oxy, thio, sulfinyl, sulfonyl, polyethyleneimine, or poly(ethylene glycol);

wherein any alkyl is optionally partially unsaturated;

wherein any aryl can optionally be substituted with one or more halo, hydroxy, nitro, cyano, (C_1-C_6)alkoxy, trifluoromethyl, polyethyleneimine, poly(ethylene glycol), oxo, NR_7R_8, wherein R_7 and R_8 are each independently hydrogen, (C_1-C_6)alkyl or polyethyleneimine; or $C(=O)OR_9$, wherein R_9 is hydrogen, (C_1-C_6)alkyl, or polyethyleneimine;

or a pharmaceutically acceptable salt thereof.

41. The method of claim 40 wherein the bond between carbons 1 and 2 is a single bond.

42. The method of claim 40 wherein the bond between carbons 1 and 2 is a double bond.

43. The method of claim 40 wherein R_1 is hydrogen.

44. The method of claim 40 wherein R_1 is hydroxy.

45. The method of claim 40 wherein R_2 is a direct bond.

46. The method of claim 40 wherein R_3 is (C_1-C_6)alkyl; wherein

any alkyl can optionally be substituted with one or more oxo, carboxy, amino, $-OP(=O)(OH)_2$, or phenyl;

any alkyl is optionally interrupted on carbon with one or more oxy or thio;

any alkyl is optionally partially unsaturated; and

any aryl can optionally be substituted with one or more hydroxy or carboxy.

47. The method of claim 46 wherein R_3 is hydroxymethyl, (carboxymethoxy)acetoxymethyl, 4-carboxybutanoyloxymethyl, 3-carboxypropenoyloxymethyl, 2-carboxybenzoyloxymethyl, 3-carboxypropanoyloxymethyl, aminoacetoxymethyl, carboxycarbonyloxymethyl, 2-amino-3-methyl-butanoyloxymethyl, 4-carboxy-(3,3-dimethyl)butanoyloxymethyl, or $-CH_2OC(=O)C(=O)-(-NHCH_2CH_2)_x-[-N(CH_2CH_2NH_2)CH_2CH_2]_y$.

48. The method of claim 40 wherein R_4 is hydrogen or $(C_1$-$C_6)$alkyl; wherein

any alkyl can optionally be substituted with one or more oxo, carboxy, amino, $-OP(=O)(OH)_2$, or phenyl;

any alkyl is optionally interrupted on carbon with one or more oxy or thio;

any alkyl is optionally partially unsaturated; and

any aryl can optionally be substituted with one or more hydroxy or carboxy.

49. The method of claim 48 wherein R_4 is hydrogen, hydroxymethyl, (carboxymethoxy)acetyl, 4-carboxybutanoyl, 3-carboxypropenoyl, 2-carboxybenzoyl, 3-carboxypropanoyl, aminoacetyl, carboxycarbonyl, 2-amino-3-methyl-butanoyl, 4-carboxy-(3,3-dimethyl)butanoyl, 3-carboxy-3-methylbutanoyl or $-C(=O)C(=O)-(-NHCH_2CH_2)_x-[-N(CH_2CH_2NH_2)CH_2CH_2]_y$.

50. The method of claim 40 wherein R_5 is oxy.

51. The method of claim 40 wherein R_4 and R_5 together are oxo.

52. The method of claim 40 wherein

R_1 is hydrogen or hydroxy;

R_2 is a direct bond;

R_3 is $(C_1$-$C_6)$alkyl;

R_4 is hydrogen or $(C_1$-$C_6)$alkyl; and

R_5 is oxy or R_4 and R_5 together are oxo;

wherein

any alkyl can optionally be substituted with one or more oxo, carboxy, amino, $-OP(=O)(OH)_2$, or phenyl;

any alkyl is optionally interrupted on carbon with one or more oxy or thio;

any alkyl is optionally partially unsaturated; and

any aryl can optionally be substituted with one or more hydroxy or carboxy.

54. The method of claim 40 wherein

R_1 is hydrogen or hydroxy;

R_2 is a direct bond;

R_3 is hydroxymethyl, (carboxymethoxy)acetoxymethyl, 4-carboxybutanoyloxymethyl, 3-carboxypropenoyloxymethyl, 2-carboxybenzoyloxymethyl, 3-carboxypropanoyloxymethyl, aminoacetoxymethyl, carboxycarbonyloxymethyl, 2-amino-3-methyl-butanoyloxymethyl, 4-carboxy-(3,3-dimethyl)butanoyloxymethyl, or $-CH_2OC(=O)C(=O)-(-NHCH_2CH_2)_x-[-N(CH_2CH_2NH_2)CH_2CH_2]_y$;

R_4 is hydrogen, hydroxymethyl, (carboxymethoxy)acetyl, 4-carboxybutanoyl, 3-carboxypropenoyl, 2-carboxybenzoyl, 3-carboxypropanoyl, aminoacetyl, carboxycarbonyl, 2-amino-3-methyl-butanoyl, 4-carboxy-(3,3-dimethyl)butanoyl, 3-carboxy-3-methylbutanoyl or $-C(=O)C(=O)-(-NHCH_2CH_2)_x-[-N(CH_2CH_2NH_2)CH_2CH_2]_y$.; and

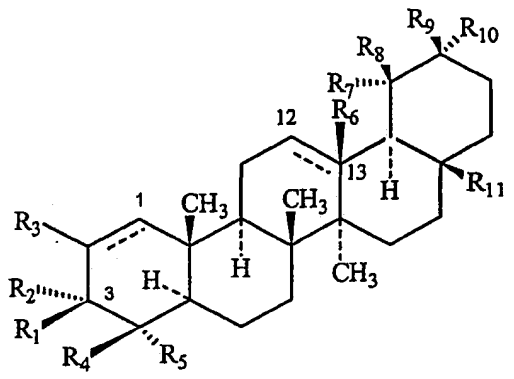
R_5 is oxy or R_4 and R_5 together are oxo.

55. The method of claim 40 wherein the triterpene is betulin; betulin-3,28-diglycine; betulin-28-glycerol oxalate; betulin-28-glycine; betulin-28-oxalate; betulin arabinose galactan; betulin-3,28-diglycolate; betulin-3-maleate; betulin-3,28-di-(L-glutamic acid γ-benzylester) ester; betulin-3,28-di-L-alanine; betulin-3,28-di-L-proline ester; betulin3,28-dioxalate; betulin-1-ene-2-ol; betulin-3,28-diphenylalanine; betulin-3,28- dioxalate-polyethylene amine; betulin-3,28-diphosphate; betulin-3-caffeate; betulin-3,28-(3',3'-dimethyl)glutarate; betulin-28-diglycolate; betulin-28-glutarate; betulin-28-maleate; betulin-28-phthalate; betulin-3,28-di(3',3'-dimethyl) glutarate; betulin-3,28-didiglycolate; betulin-3,28-dithiodiglycolate; betulin-3,28-diglutarate; betulin-3,28-dimaleate; betulin-3,28-diglycolate; betulin-3,28-diphthalate; betulin-3,28-di-L-valine ester; betulin-28-succinate; betulin-3,28-disuccinate; betulin-3,28-di-(polyethylene glycol)-COOH (Mw=1448); betulin-3,28-di-(polyethylene glycol)-COOH (Mw=906); betulin-3,28-di-(polyethylene glycol)-COOH (Mw=906); betulinic acid; betulon-1-ene-2-ol; betulin-3,28-(dipoly(ethylene glycol)bis (carboxymethylester); hederin hydrate; lupeol; lupeol-3-glutarate; lupeol-3-succinate; lupeol-3-thiodiglycolate; lupeol-3-phthalate; oleanolic acid; ursolic acid; or uvaol.

56. The method of claim 40 wherein the triterpene is betulin; betulin-3,28-diglycine; betulin-28-glycerol oxalate; betulin-28-glycine; betulin oxalate; betulin arabinose galactan; betulin-3,28-diglycolate; betulin-3-maleate; betulin di-(L-glutamic acid γ-benzylester) ester; betulin 3,28-di-L-alanine; betulin3,28-di-L-proline; betulin-3,28-dioxalate; betulin-1-ene-2-ol; betulin-3,28-diphenylalanine ester; betulin-3,28-dioxalate-(polyethylene amine); betulin-3-caffeate; betulin-3,28-(3',3'-dimethyl)glutarate; betulin-28-diglycolate; betulin-28-glutarate; betulin-28-phthalate; betulin-3,28-diglycolate; betulin-3,28-diphthalate; betulin-3,28-phosphate; betulin-28-succinate; betulin-3,28-disuccinate; betulin-3,28-di-(polyethylene glycol)-COOH (Mw=1448); betulin-3,28-di-(polyethylene glycol)-COOH (Mw=906); betulin-3,28-di-(polyethylene glycol)-COOH (Mw=906); betulon-1-ene-2-ol; betulin-3,28-(dipoly(ethylene glycol)bis(carboxymethylester); hederin hydrate; lupeol-3-succinate; lupeol-3-phthalate; lupeol-3-glutarate; oleanolic acid; ursolic acid; or uvaol.

57. The method of claim 40 wherein the triterpene is betulin; betulin-3-maleate; betulin-28-diglycolate; betulin-28-glutarate; betulin-28-maleate; betulin-28-phthalate; betulin-28-succinate; betulin-3,28-diglycine; betulin-3,28-didiglycolate; betulin-3,28-dimaleate; betulin-3,28-dioxalate-3-polyethyleneimine; betulin-3,28-di(3',3'-dimethyl)glutarate; betulin-3,28-dioxalate-3,28-polyethyleneimine; betulin-3,28-diphthalate; betulin-3,28-disuccinate; betulin-3,28-di-L-valine; lupeol; lupeol-3-amine; lupeol-3-(3',3'-dimethyl)succinate; lupeol-3-maleate; lupenone; or lupenon-1,2-ene-2-ol.

58. A method of inhibiting or killing a fungus or yeast comprising contacting the fungus or yeast with an effective anti-fungal or anti-yeast amount of a triterpene of formula (II):



(II)

wherein

one of R_1 and R_2 is -O-Y and the other is hydrogen or (C_1-C_6)alkyl optionally substituted by hydroxy, (C_1-C_6)alkoxy, halo, halo(C_1-C_6)alkoxy or NR_jR_k wherein R_j and R_k are independently H, (C_1-C_6)alkyl or (C_1-C_6)alkonyl; or R_1 and R_2 together are oxo (=O);

R_3 is hydrogen, halo, carboxy, mercapto, (C_1-C_6)alkyl, (C_3-C_8)cycloalkyl, or -O-Y;

R_4 and R_5 are each independently hydrogen, (C_1-C_6)alkyl, or hydroxy(C_1-C_6)alkyl;

R_6 is hydrogen or is absent when the adjacent --- is a bond;

R_7 is hydrogen or (C_1-C_6)alkyl;

R_8 is hydrogen, (C_1-C_6)alkyl, or hydroxy(C_1-C_6)alkyl and R_{11} is hydrogen, (C_1-C_6)alkyl, carboxy, or hydroxy(C_1-C_6)alkyl; or R_8 and R_{11} together are -O-C(=X)-;

R_9 and R_{10}, are each independently hydrogen or (C_1-C_6)alkyl;

each of the bonds represented by --- is independently absent or is present;

X is two hydrogens, oxo (=O) or thioxo (=S);

each Y is independently H, aryl, $P(O)(Cl)_2$, (C_3-C_8)cycloalkyl, adamantyl, $-SO_2R_a$ $O=P(R_b)_2$, $O=P(R_c)_2OP(O)(R_d)$-, $Si(R_e)_3$, tetrahydropyran-2-yl, an amino acid, a peptide, a glycoside, or a 1 to 10 membered branched or unbranched carbon chain optionally comprising 1, 2, or 3 heteroatoms selected from non-peroxide oxy, thio, and $-N(R_f)$-; wherein said chain may optionally be substituted on carbon with 1, 2, 3, or 4 oxo (=O), hydroxy, carboxy, halo, mercapto, nitro, $-N(R_g)(R_h)$, (C_3-C_8)cycloalkyl, (C_3-C_8)cycloalkyloxy, aryl, aryloxy, adamantyl,

adamantyloxy, hydroxyamino, trifluoroacetylamino, a glycoside, an amino acid, or a peptide; and wherein said chain may optionally be saturated or unsaturated (e.g. containing one, two, three or more, double or triple bonds);

R_a is $(C_1$-$C_6)$alkyl or aryl;

R_b, R_c, and R_d are each independently hydroxy, $(C_1$-$C_6)$alkoxy, hydroxy$(C_2$-$C_6)$alkoxy, adamantyloxy, adamantyl$(C_1$-$C_6)$alkoxy, norbornyloxy, 1,1-di(hydroxymethyl)-2-hydroxyethoxy, carboxy$(C_1$-$C_6)$alkoxy, 2,3-epoxypropyloxy, benzyloxy, $(C_3$-$C_8)$cycloalkyloxy, NR_xR_y, or aryloxy;

R_e is H, aryl or $(C_1$-$C_6)$alkyl;

R_f is hydrogen, $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$alkanoyl, phenyl or benzyl;

R_g and R_h are each independently selected from the group consisting of hydrogen, $(C_1$-$C_6)$alkyl, hydroxy$(C_1$-$C_6)$alkyl, adamantyl, adamantyl$(C_1$-$C_6)$alkyl, amino$(C_1$-$C_6)$alkyl, aminosulfonyl, $(C_1$-$C_6)$alkanoyl, aryl and benzyl; or R_b and R_c together with the nitrogen to which they are attached form a pyrrolidino, piperidino, or morpholino radical; and

R_x and R_y are each independently hydrogen, $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$alkanoyl, aryl or benzyl;

wherein each aryl of Y, R_a-R_d, R_g-R_h, R_x, and R_y may optionally be substituted by 1, 2, or 3 aminosulfonyl, carboxy, NR_iR_j, $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$alkoxy, hydroxy, halo, nitro, cyano, mercapto, carboxy, hydroxy$(C_1$-$C_6)$alkyl, halo$(C_1$-$C_6)$alkyl, trifluoromethoxy, $(C_1$-$C_6)$alkanoyl, $(C_1$-$C_6)$alkoxycarbonyl, $(C_1$-$C_6)$alkylthio, or $(C_1$-$C_6)$alkanoyloxy; wherein R_i and R_j are each independently hydrogen, $(C_1$-$C_6)$alkyl, $(C_1$-$C_6)$alkanoyl, phenyl, or benzyl;

wherein any alkyl can optionally be substituted with one or more polyethyleneimine or poly(ethylene glycol); and wherein any alkyl can optionally be interrupted with one or more polyethyleneimine or poly(ethylene glycol);

or a pharmaceutically acceptable salt thereof.

59. The method of claim 58 wherein the bond between carbons 1 and 2 is a single bond.

60. The method of claim 58 wherein R_1 is -O-Y and Y is hydrogen, an amino acid, or $(C_1$-$C_6)$alkyl; wherein

any alkyl can be optionally substituted with one or more oxo, hydroxy, amino, phenyl, or carboxy

any alky can be optionally interrupted with one or more oxy or thio;

any phenyl can be optionally substituted with one or more hydroxy or carboxy.

61. The method of claim 58 wherein R_1 is -O-Y and Y is hydrogen, 3-carboxypropanoyl, 4-carboxybutanoyl, or 2-amino-2-methylbutanoyl.

62. The method of claim 58 wherein R_2 is hydrogen.

63. The method of claim 58 wherein R_3 is hydrogen.

64. The method of claim 58 wherein R_4 is methyl.

65. The method of claim 58 wherein R_5 is methyl.

66. The method of claim 58 wherein R_6 is hydrogen and the bond between carbons 12 and 13 is a single bond.

67. The method of claim 58 wherein R_7 is hydrogen.

68. The method of claim 58 wherein R_8 and R_{11} together are -O-CH_2-.

69. The method of claim 58 wherein R_9 is methyl.

70. The method of claim 58 wherein R_{10} is methyl.

71. The method of claim 58 wherein

R_1 is -O-Y and Y is hydrogen, an amino acid, or (C_1-C_6)alkyl; wherein

the alkyl of Y can be optionally substituted with one or more oxo, hydroxy, amino,

carboxy, or phenyl optionally substituted with one or more hydroxy or carboxy;

and can be optionally interrupted with one or more oxy or thio;

R_2 is hydrogen;

R_3 is hydrogen and the bond between carbons 1 and 2 is a single bond;

R_4 and R_5 are each methyl;

R_6 is hydrogen and the bond between carbons 12 and 13 is a single bond;

R_7 is hydrogen

R_8 and R_{11} together are -O-CH_2-; and

R_9 and R_{10} are each methyl.

72. The method of claim 58 wherein the triterpene is 3-β-acetoxy-19αH-19,28 lactone oleanan; allobetulin; allobetulin-3-succinate; allobetulin-3-glycine; allobetulin lactone; allobetulin lactone-3-acetate; allobetulin lactone-3-phosphate; allobetulin-3-L-alanine; allobetulin-3-L-valine; allobetulin-3-L-proline ester; allobetulin-3-succinate; allobetulin-3-diglycolate; allobetulin-3-phthalate; allobetulin-3-methylenamine; allobetulin-3-ethanolamine; allobetulin-3-glycolate; allobetulin-3-glutarate; allobetulin-28-glutarate; allobetulin-3-methylamine HCl; allobetulin-3-phosphate; allobetulin-3-(polyethylene glycol)-COOH (Mw=674); allobetulon; allobetulon lactone 1-ene-2-ol; allobetulon lactone-1-en-2-succinate; allobetulon-1-ene-2-ol; allobetulon-1-ene-2-diglycolate; 3-allobetulon-1-ene-2-succinate; allobetulin-3-(poly(ethylene glycol)bis (carboxymethyl ester); or 3-allobetulon-1-ene-2-diglycolate.

73. The method of claim 58 wherein the triterpene is 3-β-acetoxy-19αH-19,28 lactone oleanan; allobetulin; allobetulin-3-succinate; allobetulin lactone; allobetulin lactone-3-acetate; allobetulin lactone-3-phosphate; allobetulin-3-L-valine; allobetulin-3-L-proline; allobetulin-3-succinate; allobetulin-3-diglycolate; allobetulin-3-methylenamine; allobetulin-3-ethanolamine; allobetulin-3-glycolate; allobetulin-3- glutarate; allobetulin-3-glutarate; allobetulin-3-(polyethylene glycol)-COOH (Mw=674); allobetulon; allobetulon lactone 1-ene-2-ol; allobetulon lactone-1-en-2-succinate; allobetulon-1-ene-2-ol; allobetulon-1-ene-2-diglycolate; 3-allobetulon-1-ene-2-succinate; or allobetulin-3-(poly(ethylene glycol)bis(carboxymethyl ester).

74. The method of claim 58 wherein the triterpene is allobetulin, allobetulin-3-glutarate, allobetulin-3-succinate, or allobetulin-3-L-valine.

75. The method of claim 40 or 58 wherein the fungus is a dermatophytic fungus.

76. The method of claim 75 wherein the dermatophytic fungus is *Microsporum canis*, *Microsporum gypseum*, *Microsporum audouinii*, *Trichophyton tonsurans*, *Trichophyton mentagrophytes*, *Epidermophyton floccosum*, *Trichophyton rubrum*, or *Pityrosporum ovale*.

77. The method of claim 40 or 58 wherein the fungus is *Candida albicans* or *Candida guilliermoundi*.

78. The method of claim 40 or 58 wherein the fungus is *Blastomyces dermatidis* or *Cryptococcus neoformans*.

79. The method of claim 40 or 58 wherein the yeast is *Pityrosporum ovale*.

80. The method of claim 40 or 58 wherein the contacting is in vitro.

81. The method of claim 40 or 58 wherein the contacting is in vivo.

Figure 1 of 1

Appendix II-6-2

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 01/30761

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07J63/00 A61K31/56

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07J A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, CHEM ABS Data, BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	D.K.VERMA ET AL.: "Antimicrobial Active Triperpenoids from Lantana Species" INDIAN DRUGS, vol. 34, no. 7, 1997, pages 390-2, XP002115069	17
Y	tables 1,2	1-39,80
Y	WO 00 33846 A (BOEHRINGER INGELHEIM PHARMA ;GLINSKI JAN (US); BRANLY KEITH (US);) 15 June 2000 (2000-06-15) claim 10	1-39,80
A	WO 00 46235 A (DABUR RESEARCH FOUNDATION ;KHANNA ACHLA BEHL (IN); JAGGI MANNU (IN)) 10 August 2000 (2000-08-10) claim 1	1-39

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

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Date of the actual completion of the international search	Date of mailing of the international search report
11 February 2002	18/02/2002

Name and mailing address of the ISA	Authorized officer
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INTERNATIONAL SEARCH REPORT

International Application No
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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

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